Review Article
ISSN (Print): 2455-1244
ISSN (Online): 0971-913X
J Endocrinol Reprod. *Vol 26(4), 221-237, December 2022, DOI: 10.18311/jer/2022/31013*

Epigenetic Regulation of Tamoxifen-Resistant Breast Cancer: An Update

Dibyashree Chhetri, Dhanavathy Gnanasampanthapandian and Kanagaraj Palaniyandi*

Cancer Science Laboratory, Department of Biotechnology,
School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur - 603203,
Chengalpattu, India; dhanavag@srmist.edu.in, muthammal.kanagaraj@gmail.com

Abstract

Breast cancer is the most common cause of death in women around the world. Epigenetic changes modulate transcriptional activity in several diseases, including cancer. Cancer epigenetics explains gene expression changes without DNA mutations. Aberrant DNA methylation, histone modifications, and mRNA expression promote tumor growth and metastasis. In cancer cells, chemo-resistance occurs via Multidrug Resistance (MDR), apoptotic suppression, DNA damage response, epigenetic alterations, and competitive endogenous RNA. Owing to drug resistance, quiescence, and varied cancer cell production, Cancer Stem Cells (CSCs) are critical to tumor formation, metastasis, and recurrence after therapy. In addition, MDR promotes drug efflux, enhanced secretion of growth factors, and DNA modifications in cancer patients, thereby causing fatalities in cancer patients. Heterogeneity and epigenetic plasticity cause drug resistance due to various factors. However, the molecular mechanism of epigenetic drug resistance is still unravelled completely. Overexpressed c-MYC leads to cancer and tamoxifen resistance. Despite the molecular underpinning of cancer development, drug resistance is continued in a myriad number of cases. Epigenetic changes affect CSCs viability and tumor aggressiveness. These processes can be blocked by medicines. Tamoxifen is used widely for breast cancer treatment; however, latent treatments have emerged as a tamoxifen-resistant phenotype. Epigenetic modifications cause resistance by upregulating and altering the tumor microenvironment and deregulating the immune response. The knowledge of epigenetic pathways in clinical treatment resistance may enhance the outcome of cancer patients. Multifactorial heterogeneous resistance is common in many targeted therapies. Many resistance mechanisms to targeted therapy may converge, including route reactivation. This review summarizes the epigenetic alterations, MDR, and development of tamoxifen resistance in breast cancer.

Keywords: Breast Cancer, Cancer Epigenetics, Cancer Stem Cells, Multidrug Resistance, Tamoxifen Resistance

1. Introduction

Tamoxifen has been studied extensively and is used in the primary treatment of breast cancer. Although tamoxifen has been used to treat various ailments, it has garnered a preponderant preference for the treatment of early breast cancer since its inception. Tamoxifen, established in the early 1970s, is an anti-estrogen medication. Over the past four decades, tamoxifen has been used to treat breast cancer in women throughout the globe, resulting in a 30% reduction in the death rate[1,2]. Tamoxifen is the most successful therapy and care for breast cancer; however, the resistance of cancer cells is a key downside of its use[3]. Tamoxifen is an FDA-approved selective estrogen modulator hydrophobic drug that is administered primarily to patients with postmenopausal breast cancer[4,5]. The success of tamoxifen in treating Ductal Carcinoma *In Situ* (DCIS) and the efficacy of new endocrine treatments as a tolerability profile with efficacy in both premenopausal and postmenopausal women have

*Author for correspondence

Article Received: 28.08.2022 Revised on: 19.12.2022 Accepted on: 05.01.2022

set a benchmark in cancer management. In addition, tamoxifen, administered orally, is a potential treatment for bipolar disorder[6,7]. Tamoxifen has a mechanistic involvement in bipolar disorder due to its antagonistic effects on Estrogen Receptors (ERs) in breast tissue and the suppression of Protein Kinase C (PKC)[8,9]. Tamoxifen has played a vital role in saving many lives in medical oncology and healthcare during the past few decades[10–13].

Tamoxifen reduces ER function in hormone-sensitive breast cancers by competing with estrogen for the binding of ER, thereby limiting the estrogenic actions that cause cancer formation and proliferation[14,15]. However, high-level resistance to hormone therapy has been discovered in most HIV-positive people, which results in *de novo* or acquired resistance. Therapies target estrogen synthesis or ER activation. Even though these treatments have helped a significant number of individuals, drug resistance continues to be a serious issue[16,17]. The ability to develop resistance to established therapy characterizes the disease viz., cancer, thereby resulting in higher cancer-related mortality rates[18].

Resistance is a well-known phenomenon that arises when illnesses develop resistance to therapeutic interventions. This concept was first presented when bacteria developed resistance to specific antibiotics; however, comparable processes have been observed in other diseases, including cancer[18,19]. Multidrug Resistance (MDR) is a recognized phenomenon clinically, where human tumours that develop resistance to one form of treatment develop resistance to numerous additional medications that are sometimes distinct in structure and mechanism of action[20]. Efflux of the drug in microorganisms and drug-resistant cancers is disorder-specific[18]. The discovery of MDR pathways in human cancer led to the development of therapeutic medicines to combat MDR[20]. Tamoxifen resistance is the cause of treatment failure in bone cancer cases[21]. Tamoxifen tolerance has unknown mechanisms[22]. Recently, various molecular pathways paved the way to develop tamoxifen resistance, such as receptor tyrosine kinase pathways and miRNAs[23]. Although modern chemotherapy treatment has improved, it is still ineffective against disseminated tumours. Resistance to anticancer treatments is a complex process that begins with changes in drug targets, implying the need for more targeted therapies in the therapeutic arsenal[24].

Furthermore, there is a growing body of data showing that tamoxifen has immunomodulatory effects, including findings from *in vitro* and *in vivo* trials, as well as findings from breast cancer patients who took the medication[25]. These data suggest that tamoxifen may trigger a change in immunity from cellular (T-helper 1) to humoral (T-helper 2) levels[26]. The recent crystallization of the estradiol and raloxifene ER complex provides intriguing insights with regard to anti-estrogen action and, for the first time, established a mechanism of tamoxifen drug resistance[27]. Epigenetic processes influence cancer, chromosomal imprints, gene suppression, diversification, morphogenesis, and X chromosome inactivation[28]. The resistance to cancer treatment may be influenced by epigenetic mechanisms, which are transmitted somatically during cell division. Owing to the rapid rate of epigenetic change in tumours, a diverse set of gene expression patterns may evolve as a result of medication selection throughout treatment, leading to acquired resistance[29]. Simultaneous epigenetic control of numerous genes results in the development of drug resistance in the tumours, and this has crucial implications for biomarker investigations of clinical outcomes after chemotherapy and therapeutic treatments to avoid or regulate drug resistance. As a result, new knowledge about the molecular mechanisms of tamoxifen resistance, MDR, and epigenetic regulation will aid in the development of drug resistance-fighting regimens, the discovery of novel therapeutic agents with a lower risk of developing resistance, and the development of more effective treatment strategies[30].

2. Tamoxifen

2.1 History of Development

Tamoxifen is a synthetic non-steroidal anti-estrogen developed by a team of chemists, endocrinologists, and reproductive researchers at Imperial Chemical Industries Ltd., now known as AstraZeneca, in the late 1950s[31]. Beatson hypothesized, in the late 1800s, that oophorectomy may cure invasive breast cancer in premenopausal women. Tamoxifen was used originally to treat infertility in 1966[32]. Tamoxifen became the first targeted breast cancer agent in 1972[33–37].

In 1978, tamoxifen was used mostly in postmenopausal individuals with metastatic breast cancer. Its remedial element now includes Stages I and II patients and early and late postmenopausal women[38]. Tamoxifen was designed to treat contralateral breast cancer and is being at

present studied as a chemo-preventive therapy in healthy high-risk women[22]. Recently, several articles on putative tamoxifen-resistance pathways have been published. V.C. Jordan's technique of targeted ER-positive malignancies with long-term adjuvant tamoxifen saved a large number of breast cancer patients[39–41]. Tamoxifen resistance is thought to be the result of several reasons. Knock-down of ER, upregulation of a particular growth factor receptor, stimulation of PI3K/AKT/mTOR pathway (in particular PTEN inactivation), and NF-κB signaling play important roles in tamoxifen resistance[4,42].

2.2 Tamoxifen Resistance

In the 1950s, Ethamoxytriphetol (MER-25 or Merrell) and Clomiphene citrate (Clomid, Merrell) were brought up[43]. Walpole and colleagues, in the 1960s, produced various triarylethylene derivates, which include alkyl substitutes for chlorine in clomiphene for the treatment of hormone-dependent cancers. Animal research, at the time, had suggested that clomiphene and similar chemicals caused cataracts by accumulating desmosterol, a cholesterol precursor[43,44]. Some breast cancer tumours may develop tamoxifen resistance despite its effectiveness. Clinical studies revealed that three years of intermittent treatment of tamoxifen leads to the development of tamoxifen resistance. Down-regulation, mutation, or deletion of ERs and de-escalated co-activator activation changed tamoxifen pharmacology[45,46]. Tamoxifen-induced MCF-7 tumours in nude mice may be further accelerated by estrogen, which tamoxifen inhibits, thereby implying that tamoxifen has both aggressive and antagonistic qualities in these tumours[47].

2.3 Tamoxifen: Mechanism of Action

Tamoxifen has a dual mode of action: (i) it competes with 17β-estradiol (E2) at the receptor site, reducing E2's breast cancer growth; and (ii) it binds DNA upon metabolic activation, beginning carcinogenesis. Tamoxifen competes with ER of breast cancer[48]. Tamoxifen treatment reduces the breast tumour and is associated with decreasing the serum insulin-like growth factor (IGF-1)[49] while enhancing sex hormone binding globulin (SHBG)[48,50,51]. An increase in SHBG inhibits free estradiol, which reduces tumour-promoting substances. Tamoxifen treatment kills the ERα-positive breast cancer cells[52]. Protein kinase C suppresses gene transcription, resulting in this condition[52]. Hypotheses explaining tamoxifen's apoptotic activity include a threefold spike in cytoplasmic and mitochondrial calcium ions or TGF-β production[52,53].

Tamoxifen functions as an estrogen agonist and antagonist in different parts of the body. It binds to ERs preferentially, producing both estrogenic and anti-estrogenic effects; as a specific ER modulator, it is patient-specific due to its binary conditioning[54]. It competes with estrogen in breast tissue, causing anti-estrogenic and anticancer effects. Intracellular processes impede cell cycle progression. It boosts rather than inhibits ER in bone, which may avoid fractures in postmenopausal women[55]. It also works as an estrogen agonist in premenopausal women's hypothalamus, thereby increasing gonadotropin levels and causing ovulation. Tamoxifen is metabolized in the liver by a role to CYP450 enzymes such as 2B6, 2C9, 2C19, 2D6, and 3A4. The half-life of tamoxifen is 5–7 days and N-desmethyl tamoxifen is 14 days[56,57].

The estrogen–ER complex homodimerizes and attaches to estrogen response elements in estrogen-sensitive genes. AF1 and AF2 (transcriptional co-activators) bind with other molecules to boost RNA Pol II activity and control gene activity[58]. Tamoxifen competes with estrogen for ER binding[59]. Tamoxifen–ER complexes bind to estrogen-sensitive genes and form homodimers[58]. However, only if AF1 is operational while on tamoxifen-ER binding[60]. When AF2 is inactive, estrogen-responsive gene transcription and co-activator binding are diminished. As a consequence, tamoxifen slows cell growth by blocking the G1 phase of the cell cycle. Tamoxifen may have several modes of action, tamoxifen may affect breast cancer epithelial cells indirectly by altering cytokine levels both locally and systemically[61]. It increases the generation of TGF-β, which inhibits breast cancer cells[61,62]. Tamoxifen suppresses IGF-1, an anti-angiogenic breast cancer mitogen[63,64]. Tamoxifen binds to non-specific sites as well as particular binding sites[65].

3. Mechanisms of Resistance: Endocrine Therapy

Significant advancements in the treatment of early breast cancer have been observed during the past 25 years. One of the most significant achievements in respect of hormone receptor-positive breast cancers is the widespread use of Endocrine Therapy (ET) similar to tamoxifen, a specific selective ER modulator, or Aromatase Inhibitors (AIs),

both nonsteroidal analogous (such as letrozole) and anastrozole or steroidal comparable (such as exemestane), which block estrogen production[66]. The resistance that develops during therapy might be inherent, which means that it exists before the commencement of the treatment or is acquired during the treatment[46,67].

4. Estrogen Receptor

Estradiol (E2) binds to ER, a ligand-activated key transcription that interacts with estrogen response elements (EREs) in nonsupervisory regions of its target genes[68,69]. ER may homo- (ERα-ERα) or heterodimerize (ERα-ERβ) to interfere with transcriptional activity, which is encoded by genes on chromosomes 6 and 14. Each ERα/ERβ subtype regulates genes differently, expresses differently in different cells and tissues, and influences various downstream signalling cascades[70]. ER activation enhances tumorigenesis by proliferating and invading breast cancer cells. ER reduces cell proliferation, decreases epithelial-to-mesenchymal transition, and boosts tamoxifen sensitivity[71,72]. High ER levels in individuals without ER are related to higher survival and tamoxifen response, whereas low ER levels may lead to endocrine treatment resistance[73,74]. ER amplification in tamoxifen-resistant women's pre-invasive metastatic breast cancer seems to inhibit ER-stimulated transcription.

Both ERα and ERβ subtypes may vary in the regulation of gene expression, cellular location, and cancer pathogenicity[75]. When compared with the full-length ER protein, at least two docked ER isoforms (ER36 and ER46), which result from alternative splicing, exon deletion, and promoter activity, act in a dominant negative manner[76,77]. In endometrial cells, ER36 was limited to the mitochondrial matrix, had no genetic activities, and was associated with tamoxifen resistance; however, ER46 increased tamoxifen perceptivity in tamoxifen-resistant MCF-7 cells. On the basis of the removal of exon 8, ER comprises many isoforms similar to ER1 (full-length), known as ER2 to ER5. Nuclear ER2 and ER5 have been shown to decrease ER function while promoting ER1 transactivation. As they are co-expressed consistently with ER[78], their relevance to endocrine resistance is being investigated at present. As ER subtypes push and pull, their percentage is being examined as a diagnostic tool for endocrine drug response[79]. Owing to a paucity of adequate antibodies, subtype data are questionable[80]. Large quantities of tyrosine kinase receptors, signalling proteins, and ER are predicted in caveolae and lipid rafts[81,82]. In tamoxifen-resistant cells, ER relocation increases epidermal growth factor receptor (EGFR) binding and downstream signalling. Another endocrine resistance media is characterized most probably in this manner[83] (Figure 1).

4.1 Estrogen Receptor Alteration

A possible tamoxifen resistance mechanism for ER protein structural alterations results in the altered affinity of the receptor. Defects in the ER gene encoding may cause aberrant receptors physically. These mutations may inactivate the ER, giving the tumour an ER-negative look. If mutations affect critical receptor amino acids, functionally active ER species with distinct estrogen and tamoxifen specificities may arise[22]. There are innumerable studies reporting that mutations and mRNA splice variants in *ERα* result in tamoxifen resistance[84–86].

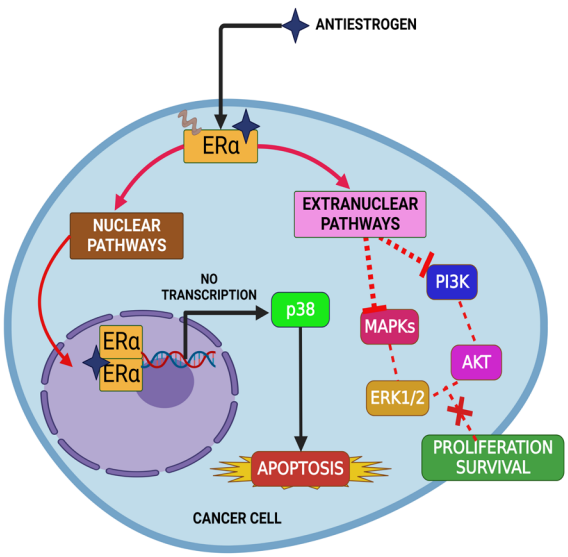

Figure 1. Anti-estrogens, which are estrogen blockers, function by inhibiting the Estrogen Receptor (ER) either by inhibiting its nuclear pathways or by inhibiting the extranuclear pathways. In the nuclear pathway, anti-estrogen binds to the ERα dimer preventing it from transcribing, thereby leading to cell apoptosis. In the extranuclear signaling pathways, the cell survival of the cancer cells inhibited by blocking via MAPKs, PI3K, ERK1/2, and AKT signaling molecules.

4.2 Estrogen Receptor Cofactors

ER is a modulator protein containing an N-terminal transactivation domain (AF1), and a C-terminal Ligand Binding Domain (LBD). Co-activators/co-repressors, and transcriptional and histone modifiers comprise the bound ER[87]. When ligand is bound, helix5 and 12 create a hydrophobic pocket and protein surface for interacting with co-activator LXXLL motifs[87]. Tamoxifen binds to the same regulatory sites as estrogen-bound ER, but shifts helix 12 away from the ligand binding pocket, which leads tamoxifen-bound ER to employ a co-repressor group rather than a co-activator group to counterbalance hormone response[88,89].

High levels of ER co-activators, such as amplification in ER co-activator (AIB1), have been established to augment tamoxifen's agonist effect and contribute to tamoxifen resistance[87,90]. Tamoxifen's agonistic actions on the ER were exacerbated by a prolonged decrease in nuclear receptor co-repressor 1, and co-repressor activity during tamoxifen therapy, which increases tamoxifen resistance[91]. ER's non-classical genomic effects include indirect DNA binding. Membrane-bound non-classical signalling activates MAPK and G-protein-coupled receptor activation leading to the induction of mitogenesis[92]. Tamoxifen–ER antagonist activity is transformed into an aggressive action as a result of these complexes, which influences breast cancer cell proliferation[93]. An increase in the expression of these factors has also been linked to endocrine treatment resistance[94]. SRY-box 9 (SOX9) is a stem cell factor that promotes mitosis, migratory phenotype, and endocrine treatment resistance[95]. FOXA1 co-expresses with ERα throughout mammary gland development and early breast cancer formation[69,96]. Over-expressed FOXA1 stimulates tumorigenesis and endocrine resilience proteins, including IL-8[97].

Endocrine resistance is also fueled by non-ER-dependent reprogramming chromatin landscapes. EZH2, a chromatin-altering enzyme, confers endocrine treatment resistance by reducing GREB1, an ER cofactor. EZH2 is high in tamoxifen-resistant samples, and low GREB1 changes the ER transcriptional machinery and transcript, which leads to resistive phenotypes in hormone-positive cells[95]. In another research, drug-sensitive MCF-7 cell lines have different open chromatin landscapes[98]. Traditional ER signalling had no discernible benefit in these cell lines. Nonetheless, chromatin remodelling enriches and over-expresses the NOTCH network and some other molecular targets in resistant cells, with NOTCH3 responsible for resistance. NOTCH3-activated PBX1 induces endocrine resistance genes[98]. The crosstalk of PKC-α and Notch-4 signalling induces tamoxifen resistance in breast cancer[99]. Recently, the over-expression of Notch-1 has been associated with the development of tamoxifen resistance and MDR in breast cancer[100].

4.3 Estrogen Receptor and its Signaling Pathways

Post-translational modifications to the wild-type ER protein result in ligand-independent ER activation consistently. Growth factor signalling protein over-expression alters the ER, making the cell tamoxifen resistant. The phosphorylation of the ERα is due to the over-expression of receptor tyrosine kinases corresponding to HER2, EGFR, and IGF1R[101–103]. Phosphorylation activates the ER in the absence of a ligand, rendering cells tamoxifen resistant. Endocrine resistance has also been connected to MAPK or the PI3K/AKT signalling pathway activation[105]. Furthermore, HER2 transfection in hormone receptor–positive cells down-regulates ERα, thereby providing resistance to anti-hormone treatment[105,106]. c-Jun/AP1 exerted over-expression and reduced the sensitivity of tamoxifen treatment in ERα-positive breast cancers[107]. Interluekin-6 (IL-6) potentiates the ERα signalling and activates cell proliferation in MCF-7 breast cancer cells[108].

5. Acquired Tamoxifen Resistance: Potential Mechanisms

Several pathways have been connected to the development of acquired resistance to tamoxifen. Many of the proposed processes, on the other hand, have no conclusive evidence to back them up. Tamoxifen has been found in *in vitro* and *in vivo* studies to promote cell proliferation after prolonged exposure[65,109]. The ability of tamoxifen to select a sub-clone of tamoxifen-stimulated cells changes tamoxifen in such a way that the cells release a stimulatory signal or generate a genetic mutation, which increases unknown drug sensitivity. Tamoxifen has been discovered to form DNA adducts in the liver of rats, implying that it may have genotoxic qualities that cause mutations[110].

Even though the mechanisms which cause tamoxifen resistance are unknown, recent research suggests that many pathways are implicated. Changes in ER levels, lower ER affinity, enhanced cellular mechanisms for avoiding

Tamoxifen cytotoxicity, reduced cellular tamoxifen level, enhanced levels of antagonizing metabolites, and other routes have helped to understand tamoxifen resistance[22].

6. Mechanisms: Anti-Estrogen Resistance

Several processes have been linked to the development of tamoxifen resistance. However, many of the postulated processes have little solid evidence to back them up. Drugs were once thought to be responsible for causing metabolic changes in cells that resulted in drug resistance.

Tamoxifen is thought to limit tumour cell proliferation primarily by interacting with ER[22]. Recent data from breast cancer biopsies link tamoxifen resistance to altered growth factor receptor expression and downstream signalling cascades[17]. Kinases downstream of these receptors, such as ERK1/2, p38, AKT, and p21-activated kinase-1, are active consistently in nonresponsive cancers with *de novo* or acquired resistance[111–115]. In tamoxifen-resistant tumors, BCAR1, AIB1, and ERα expression are all elevated significantly. Tamoxifen reduces estrogen-dependent cancer cell growth by preventing G0/G1 phase[116]. Interaction tamoxifen with the receptor is thought to result in the formation of a complex that, when linked with estrogen-responsive regions, stops target genes from being transcribed. The ensuing blockage is thought to be cytostatic mostly, and it can be reversed by adding estradiol. It is still unclear whether tamoxifen causes apoptosis or cell death.

Tamoxifen's anti-estrogenic actions differ with species and target tissues. Rats and humans have tamoxifen sensitivity. Tamoxifen has estrogen-agonist effects in uterine tissues; however, it is an estrogen inhibitor in most instances[117]. Tamoxifen affects postmenopausal gonadotropin levels, plasma proteins, and vaginal epithelium[116–118]. It is not known if the variation in the anti-estrogenic effect is due to species or tissue-specific tamoxifen metabolism or different transcription factors that modify signal interpretation by the cell after the anti-estrogen interacts with the ER. Numerous other factors would still influence the cellular response of tamoxifen.

Tamoxifen was also found to bind to non-ER locations[119]. The digestive system, uterus, ovaries, brain, and kidneys have the most estrogen-binding sites and Anti-Estrogen Binding Sites (AEBS)[120]. The AEBS are different from the ER and emerge only after estradiol therapy[119]. Anti-estrogen affinity for AEBS does not appear to be related to the biological efficacy of anti-estrogen, which implies that AEBS does not mediate anti-estrogen activity directly[121,122]. Many investigations have linked AEBS binding to anti-estrogen-related physiological activities, such as protein kinase C inhibition[123], calmodulin inhibition[124], and interactions with histamine[125], dopamine[126], and muscarinic receptors[127]. AEBS have generated interest consistently, although their role in the antitumor efficacy of tamoxifen is uncertain.

Several studies have shown that ERβ is lost during carcinogenesis, which indicates that it may play a tumour-suppressing role[128,129]. When both receptors are expressed, ERβ has been found to reduce ERα's function as a transcriptional activator while promoting anti-proliferative and pro-apoptotic activities[128,130]. Numerous genes controlled by ERβ, but not ERα, have been found; and researchers are determining whether these transcripts have anti-proliferative or pro-apoptotic features that might explain ERβ's tumour suppressor function[128,131,132].

7. Multidrug Resistance

Drug inactivation and inhibition are caused by various indigenous and foreign factors, including cellular reprogramming, neoplastic stimulation, drug efflux due to the over-expression of MDR genes, and metabolic changes. Changes in indigenous and external stimuli result in the DNA damage repair mechanism, evasion of programmed cell death, and epithelial–mesenchymal translocation[133–135]. The unpredictability of the acquired cell death evasion strategies of the cancer cells may also compromise immune surveillance[136]. Furthermore, the link between cancer and oxidative stress has been investigated thoroughly, which indicates that ROS plays a crucial role in cancer progression[137]. An imbalance in redox homeostasis is a key element in the development of cancer treatment resistance. As oxidative stress is important for cell survival, it may also contribute to cancer medication resistance[138].

Single-Agent Resistance (SAR) or MDR might be confined to the medicine that is used to treat a patient.

Owing to its ability to disrupt the expected medication response in cancer patients, resistance to several treatments during cancer therapy has been a "clinician's nightmare." As a result, dealing with drug resistance in a cancer treatment program is difficult[100,139].

8. Mechanisms of Drug Resistance

An increase in the expression of ATP-Binding Cassette (ABC) carrier proteins, which export substrates across the cell membrane through ATP hydrolysis, drives cancer therapy resistance[140]. These drug efflux transporters decrease the cellular concentration of the drug and compromise treatment responsiveness[141]. Research links 48 ABC transporters to humans[142]. Many of them protect the kidney, pancreas, liver, GI tract, testes, and brain endothelial arteries[143]. There are 13 ABC transporters are linked to cancer therapy resistance. ABCB1 (permeability glycoprotein/ MDR1)[144], ABCC1 (MDR related protein-1, MRP1), and ABCG2/BCRP (breast cancer resistance protein) have been studied carefully to better understand multidrug resistance. ABC transporters are involved in the removal of xenobiotics and harmful endogenous chemicals from cells and organs in order to maintain interstitial equilibrium. These membrane-bound transporters are used by cancer cells to develop drug resistance[145]. Domains were constructed by utilizing Illustrator of Biological Sequences, and these sequences were acquired from Uniprot Database[146,147].

In the processes of these ABC transporters, ATP plays a significant role. ATP levels in drug-resistant cancer cells are higher than in parental cancer cells[148]. When ATP levels are low, cancer cells become much more susceptible to treatment. Drug-sensitive cells become drug-resistant as their intracellular ATP concentrations increase[149]. Extracellular ATP also promotes the expression of ABC transporters, resulting in increased drug efflux[150]. Extracellular ATP concentrations are known to increase the tumour microenvironment[133]. With the help of a mechanism known as "macropinocytosis," cancer cells consume this extracellular ATP. Numerous chemotherapeutic drugs become resistant as a result of the considerable increase in intracellular ATP concentration[151]. Accumulating evidence has shown the combination of therapies in tamoxifen-resistant cancer, a higher opportunity to develop MDR, and stem-like phenotypes in breast cancer[100,139,152].

9. Drug Resistance and Epigenetics

Epigenetics determines cell destiny and pathogenic provenience. Nongenetic heterogeneity causes tumour-initiating cells and/or therapy resistance. Epigenetic changes produce inadequate gene expression, which lasts across cell cycles and contributes to nongenetic variation and resistance to treatment[153].

Precision oncology benefits from epigenetic-based diagnostic and prognostic techniques substantially. Numerous genetic diagnostic tests are in clinical studies or usage[154]. Epidrugs, or drugs that target epigenetic modulators, were developed as a result of precision oncology efforts to address dysregulated epigenetic pathways[155].

Epigenetic modifications govern gene transcription via altering chromatin packaging and regulate DNA accessibility to sequence-specific transcription factors. Genetic variation, chromatin rearrangement, histone modification, and non-coding RNA alterations are linked to cancer chemoresistance[155,156] (Figure 2).

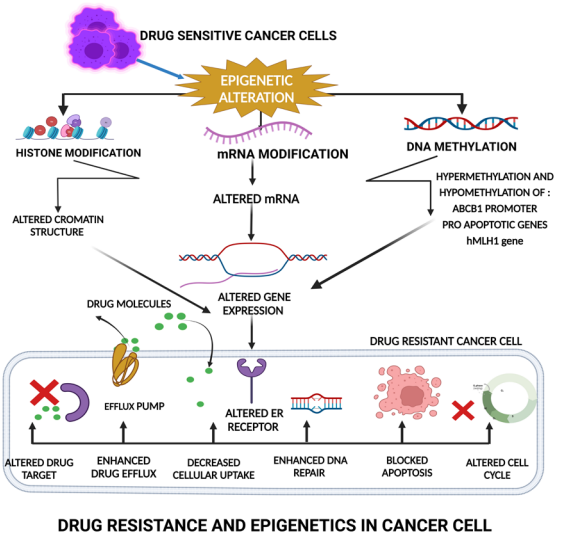

Figure 2. Drug-sensitive cancer cells upon epigenetic alterations lead to histone modification, methylation, and mRNA modification, which lead to altered gene expression. These alterations in gene expression lead to drug target site alteration, cell cycle and ER receptor alteration, decreased cellular uptake, enhanced drug efflux, blocked apoptosis, and enhanced cellular repair; thereby, making the drug-sensitive cancer cell resistant to the drug.

10. Molecular Mechanism

Aberrant modification of CpG islands around gene promoter regions induces gene silencing during tumour development, as governed by molecular mechanisms[157]. DNA methylation is associated with Histone Deacetylases (HDACs), chromatin condensation, and gene silencing[158]. The frequency of epimutations is far larger than that of genetic mutations. According to the study, 61 unusual mutations were detected during metastasis, 15 of which were driver genes and the rest were altered passenger genes. As a result, these modifications have a smaller impact on sub-population selection related to tumour formation and medication resistance. According to the accumulated evidence, demethylation of the MDR1 protagonist appears to be associated with (MDR) in a range of tumour types[159,160]. Epigenetic alterations improve DNA damage repair in cancer cells by reviving the DNA repair molecule MGMT, which enhances the survival of malignant cells. Cancer cells affect the sensitivity to modification and epigenetic suppression of proapoptotic genes, such as *APAF1* and *hMLH1*, and oncogenes and tumour suppressor genes, such as *BRCA1* and *E-cadherin.* Exosomes are also thought to have a role in epigenetic alterations, according to recent research[161]. According to another recent study, exosomes are considered to play a role in tumour growth, cell proliferation, and metastasis. Extracellular vesicles carry proteins and nucleic acids to target cells, affecting chromatin alteration, chromatin structure, and RNA post-transcriptional control[162]. Tumour microenvironment fibroblasts and immunocytes release exosomes where they transport a range of loadings and microRNAs (miRNAs). Exosomal miRNAs intervene in drug resistance mechanisms, such as medicine efflux, medication metabolism changes, drug target mutations, DNA repair, metabolic alterations, cancer stem cells, and epigenetic modifications[163]. Exosomal miRNAs promote resistance to medication.

11. ERα Signaling and Epigenetics

Estradiol activates ER target sites, which recruit hundreds of ER co-regulators to chromatin to ensure optimum transcriptional and repressive activity. Even though each ER molecule resides on chromatin for only seconds, it cycles on and off for minutes and hours after estradiol stimulation. ER receptor coactivators such as P300/CBP, SWI/SNF and PRMTs, are activates the epigenetic changes associated with them. SRC-1, SRC-2, and SRC-3 attach to ER physically and serve as a platform for ER to recruit additional stimulating kinases and chromatin remodelling complexes[164]. P300, a histone acetyltransferase (HAT), communicates with ER-bound enhancers through SRC-3 to acetylate histone H3 lysine 27 (H3K27ac), thereby activating enhancers[165,166]. Estradiol elevates H3K27ac concentrations at loci in which the ER has a regulatory effect[167–169]. An increase in the H3K27ac at ER-bound enhancers corresponds with BRG1, the SWI/SNF catalytic element, which shows that ER promotes the SWI/SNF complexes to redesign and activate enhancers[170] NCoR1, NCoR2, and LCoR engage with an epigenetic suppressor to down-regulate estradiol-repressed genes[171]. The ER corepressor BRCA1 is well-known. After binding to the AF2 area, BRCA1 monoubiquitinates the ER, thereby decreasing its transcriptional activity[168]. The transcriptional and oncogenic effects of these coregulators have been well-studied[172–174]. Estradiol-dependent ER recruitment requires colonial transcription factors. Pioneer transcription factors in ER breast cancer have been studied[169]. GRHL2 shows numerous functional similarities to FOXA1 and GATA3, including estradiol-independent chromatin assembly and ER target gene regulation[170,171,175]. PRC1 and PRC2 increase estradiol-induced ER corresponding transcriptional activation in breast cancer cells by recruiting chromatin[168,176–178]. Polycomb complexes have also been discovered to have both repressive and activating effects in stem cells, embryonic development, and cancer cells, as well as the activities that take place inside these cells[176]. The roles of GRHL2 and polycomb-group proteins as ER signalling regulators in ER+ breast cancers require further investigation (Figure 3).

12. Future Research Directions of Tamoxifen in Cancer Treatment

Tamoxifen is a potent anticancer drug that plays a vital role in ER-positive breast cancer patients. The main drawback of this drug is its drug resistance, which most probably limits its efficacy, thereby emphasizing the importance of overcoming tamoxifen resistance in breast cancer. The methods to overcome breast cancer resistance are based on the major mechanism of drug resistance. Mechanistic pathways are inhibited, such

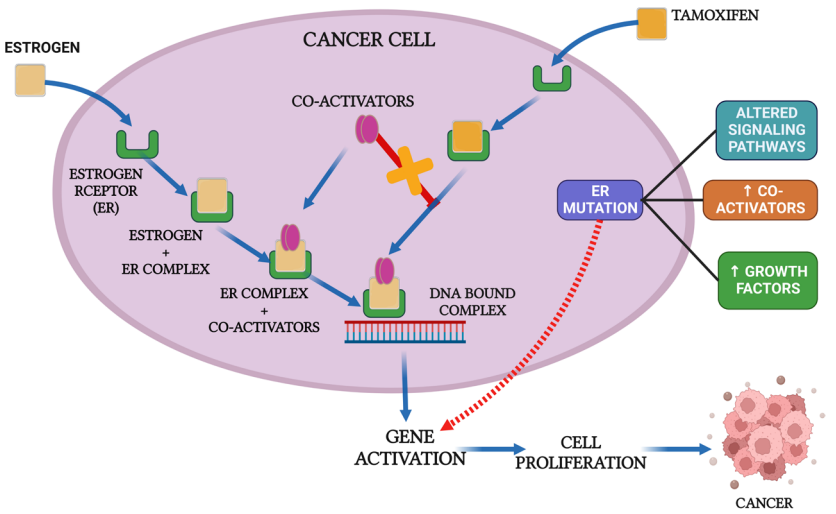

Figure 3. Tamoxifen is an estrogen competitor that competes for the active site on the Estrogen Receptor (ER) and blocks estrogen from binding to its receptor. Tamoxifen functions as an anti-estrogen by inhibiting the co-activators that bind with the ER complex. Upon tamoxifen binding, transcription of the ER complex is inhibited, as a result of which cancer cell growth and proliferation cease. However, an increase in the number of growth factors, co-activators, and altered pathways lead to alterations in ER and, ultimately, led to cancer cell formation.

as the RTK pathway, blocking protective autophagy, upregulation of ERα36, cell cycle regulators, and EMT-like specific phenomenon. Some novel methods have broadened our vision to overcome the drug resistance of tamoxifen totally, by using combinational drug therapy with other drugs that can inhibit the development of drug resistance. In recent years, most of the research on the relationship among the major areas of autophagy, cell cycle regulators, and tamoxifen resistance has made great progress. Hence, these methods to overcome drug resistance by inducing autophagy mechanisms are limited most probably in the current research due to the inhibition of autophagy by its inhibitors.

The continued search for better autophagy inhibitors to overcome the resistance has thrown light to hypothesize that tamoxifen combined with other drugs may protect the mitochondrial function which in turn enhanced autophagy and overcome the drug resistance of tamoxifen. This view is a new arena to improve the drug resistance of tamoxifen, and more research studies are needed to explore a clear view in this field. The main target to overcome tamoxifen resistance is to target LEM4, which is a feasible direction for research in the future. It is already evident that the high expression of LEM4 in drug-resistant cells is an important biological mechanism involved in the attenuation of the inhibitory effect of tamoxifen on the G1–S transition. Hence, targeting LEM4 will play a potent role in overcoming tamoxifen resistance in breast cancer and will be an important tool in the future.

13. Conclusion

Tamoxifen treatment epigenetically altered gene expression associated with changes in coregulators, epigenetics and post-translational changes, and genetic variations in the ER pathway may cause endocrine resistance. "Epigenetic treatment," which appears to be promising, could be a solution to the problem of medication resistance in the cancer field. HDAC inhibitors, for example, have shown the potential to lower antiestrogen-resistant cell proliferation.

Finally, new information has emerged on the possible routes that contribute to tamoxifen resistance. Tamoxifen-resistant animals or patients show ER loss or alterations, decreased intracellular tamoxifen concentrations, and altered metabolite profiles, according to various scientific investigations. According to recent studies, breast cancer

cells become MDR and stem-like due to the treatment with tamoxifen. Research into epigenetic regulation in MDR and tamoxifen resistance can potentially lead to new cancer treatment regimens, which will improve patient outcomes.

14. Acknowledgement

We would like to thank Mr. M. Vijayaraman for editing the English language.

15. References

1. Hackshaw A, Roughton M, Forsyth S, *et al.* Long-term benefits of 5 years of tamoxifen: 10-year follow-up of a large randomized trial in women at least 50 years of age with early breast cancer. J Clin Oncol. 2011; 29(13):1657-63. https://doi.org/10.1200/JCO.2010.32.2933 PMID:21422412
2. Chlebowski RT, Aragaki AK, Pan K. Breast cancer prevention: Time for change. JCO Oncology Practice. 2021; 17(12):709-16. https://doi.org/10.1200/OP.21.00343 PMID:34319769 PMCID:PMC8677965
3. Yao J, Deng K, Huang J, *et al.* Progress in the understanding of the mechanism of tamoxifen resistance in breast cancer. Front Pharmacol. 2020; 11:592912. https://doi.org/10.3389/fphar.2020.592912 PMID:33362547 PMCID:PMC7758911
4. Ali S, Rasool M, Chaoudhry H, *et al.* Molecular mechanisms and mode of tamoxifen resistance in breast cancer. Bioinformation. 2016; 12(3):135-9. https://doi.org/10.6026/97320630012135 PMID:28149048 PMCID:PMC5267957
5. Day CM, Hickey SM, Song Y, *et al.* Novel tamoxifen nanoformulations for improving breast cancer treatment: Old wine in new bottles. Molecules. 2020; 25(5). https://doi.org/10.3390/molecules25051182 PMID:32151063 PMCID:PMC7179425
6. Bebchuk JM, Arfken CL, Dolan-Manji S, *et al.* A preliminary investigation of a protein kinase C inhibitor in the treatment of acute mania. Arch Gen Psychiatry. 2000; 57(1):95-7. https://doi.org/10.1001/archpsyc.57.1.95 PMID:10632242
7. Yatham LN, Kennedy SH, Parikh SV, *et al.* Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018; 20(2):97-170. https://doi.org/10.1111/bdi.12609 PMID:29536616 PMCID:PMC5947163
8. Jordan VC. Molecular mechanisms of antiestrogen action in breast cancer. Breast Cancer Res Treat. 1994; 31(1):41-52. https://doi.org/10.1007/BF00689675 PMID:7981455
9. Manji HK, Zarate CA. Molecular and cellular mechanisms underlying mood stabilization in bipolar disorder: Implications for the development of improved therapeutics. Mol Psychiatry. 2002; 7 Suppl 1:S1-7. https://doi.org/10.1038/sj.mp.4001068 PMID:11986989
10. Jordan VC. Tamoxifen: a most unlikely pioneering medicine. Nat Rev Drug Discov. 2003; 2(3):205-13. https://doi.org/10.1038/nrd1031 PMID:12612646
11. Fisher B, Costantino JP, Wickerham DL, *et al.* Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 2005; 97(22):1652-62. https://doi.org/10.1093/jnci/dji372 PMID:16288118
12. Dhingra K. Antiestrogens--tamoxifen, SERMs and beyond. Invest New Drugs. 1999; 17(3):285-311. https://doi.org/10.1023/A:1006348907994 PMID:10665480
13. Grainger DJ, Metcalfe JC. Tamoxifen: Teaching an old drug new tricks? Nat Med. 1996; 2(4):381-5. https://doi.org/10.1038/nm0496-381 PMID:8597938
14. Banerjee S, Saxena N, Sengupta K, *et al.* 17alpha-estradiol-induced VEGF-A expression in rat pituitary tumor cells is mediated through ER independent but PI3K-Akt dependent signaling pathway. Biochem Biophys Res Commun. 2003; 300(1):209-15. https://doi.org/10.1016/S0006-291X(02)02830-9 PMID:12480545
15. Chang XZ, Li DQ, Hou YF, *et al.* Identification of the functional role of peroxiredoxin 6 in the progression of breast cancer. Breast Cancer Res. 2007; 9(6):R76. https://doi.org/10.1186/bcr1789 PMID:17980029 PMCID:PMC2246172
16. Rasha F, Sharma M, Pruitt K. Mechanisms of endocrine therapy resistance in breast cancer. Mol Cell Endocrinol. 2021; 532:111322. https://doi.org/10.1016/j.mce.2021.111322 PMID:34000350
17. Riggins RB, Schrecengost RS, Guerrero MS, *et al.* Pathways to tamoxifen resistance. Cancer Lett. 2007; 256(1):1-24. https://doi.org/10.1016/j.canlet.2007.03.016 PMID:17475399 PMCID:PMC2533271
18. Housman G, Byler S, Heerboth S, *et al.* Drug resistance in cancer: An overview. Cancers (Basel). 2014; 6(3):1769-92. https://doi.org/10.3390/cancers6031769 PMID:25198391 PMCID:PMC4190567
19. Bolhuis H, van Veen HW, Poolman B, *et al.* Mechanisms of multidrug transporters. FEMS Microbiol Rev. 1997; 21(1):55-84. https://doi.org/10.1111/j.1574-6976.1997.tb00345.x PMID:9299702

20. Baguley BC. Multiple drug resistance mechanisms in cancer. Mol Biotechnol. 2010; 46(3):308-16. https://doi.org/10.1007/s12033-010-9321-2 PMID:20717753
21. Chang YC, Cheung CHA, Kuo YL. Tamoxifen Rechallenge decreases metastatic potential but increases cell viability and clonogenicity in a tamoxifen-mediated cytotoxicity-resistant subline of human breast MCF7 cancer cells. Front Cell Dev Biol. 2020; 8:485. https://doi.org/10.3389/fcell.2020.00485 PMID:32695778 PMCID:PMC7338790
22. Wiebe VJ, Osborne CK, Fuqua SAW, *et al*. Tamoxifen resistance in breast cancer. Critical Reviews in Oncology/Hematology. 1993; 14(3):173-88. https://doi.org/10.1016/1040-8428(93)90008-R PMID:8397846
23. Garcia-Becerra R, Santos N, Diaz L, *et al*. Mechanisms of resistance to endocrine therapy in breast cancer: focus on signaling pathways, miRNAs and genetically based resistance. Int J Mol Sci. 2012; 14(1):108-45. https://doi.org/10.3390/ijms14010108 PMID:23344024 PMCID:PMC3565254
24. Shah K, Rawal RM. Genetic and epigenetic modulation of drug resistance in cancer: challenges and opportunities. Curr Drug Metab. 2019; 20(14):1114-31. https://doi.org/10.2174/1389200221666200103111539 PMID:31902353
25. Corriden R, Hollands A, Olson J, *et al.* Tamoxifen augments the innate immune function of neutrophils through modulation of intracellular ceramide. Nat Commun. 2015; 6:8369. https://doi.org/10.1038/ncomms9369 PMID:26458291 PMCID:PMC4610010
26. Behjati S, Frank MH. The effects of tamoxifen on immunity. Curr Med Chem. 2009; 16(24):3076-80. https://doi.org/10.2174/092986709788803042 PMID:19689284 PMCID:PMC2902982
27. Levenson AS, Wolf DM, Catherino WH, *et al*. Understanding the antiestrogenic actions of raloxifene and a mechanism of drug resistance to tamoxifen. Breast Cancer. 1998; 5(2):99-106. https://doi.org/10.1007/BF02966681 PMID:11091634
28. Badia E, Oliva J, Balaguer P, *et al*. Tamoxifen resistance and epigenetic modifications in breast cancer cell lines. Curr Med Chem. 2007; 14(28):3035-45. https://doi.org/10.2174/092986707782794023 PMID:18220739 PMCID:PMC2789301
29. Brown R, Curry E, Magnani L, *et al*. Poised epigenetic states and acquired drug resistance in cancer. Nat Rev Cancer. 2014; 14(11):747-53. https://doi.org/10.1038/nrc3819 PMID:25253389
30. Chang M. Tamoxifen resistance in breast cancer. Biomol Ther (Seoul). 2012; 20(3):256-67. https://doi.org/10.4062/biomolther.2012.20.3.256 PMID:24130921 PMCID:PMC3794521
31. Jordan VC. The development of tamoxifen for breast cancer therapy: A tribute to the late Arthur L. Walpole. Breast Cancer Res Treat. 1988;11(3):197-209. https://doi.org/10.1007/BF01807278 PMID:3048447
32. Harper MJ, Walpole AL. Contrasting endocrine activities of cis and trans isomers in a series of substituted triphenylethylenes. Nature. 1966; 212(5057):87. https://doi.org/10.1038/212087a0 PMID:5965580
33. Jordan VC. Tamoxifen (ICI46,474) as a targeted therapy to treat and prevent breast cancer. Br J Pharmacol. 2006; 147(Suppl 1):S269-76. https://doi.org/10.1038/sj.bjp.0706399 PMID:16402113 PMCID:PMC1760730
34. Jordan VC. Effect of tamoxifen (ICI 46,474) on initiation and growth of DMBA-induced rat mammary carcinomata. European Journal of Cancer (1965). 1976; 12(6):419-24. https://doi.org/10.1016/0014-2964(76)90030-X
35. Jordan VC, Allen KE. Evaluation of the antitumour activity of the non-steroidal antioestrogen monohydroxytamoxifen in the DMBA**DMBA; 7,12-dimethylbenz(a)anthracene.-induced rat mammary carcinoma model. European Journal of Cancer (1965). 1980; 16(2):239-51. https://doi.org/10.1016/0014-2964(80)90156-5
36. Jordan VC. Tamoxifen as the first targeted long-term adjuvant therapy for breast cancer. Endocr Relat Cancer. 2014; 21(3):R235-46. https://doi.org/10.1530/ERC-14-0092 PMID:24659478 PMCID:PMC4029058
37. Jordan VC. Tamoxifen: catalyst for the change to targeted therapy. Eur J Cancer. 2008; 44(1):30-8. https://doi.org/10.1016/j.ejca.2007.11.002 PMID:18068350 PMCID:PMC2566958
38. Buchanan RB, Blamey RW, Durrant KR, *et al*. A randomized comparison of tamoxifen with surgical oophorectomy in premenopausal patients with advanced breast cancer. J Clin Oncol. 1986; 4(9):1326-30. https://doi.org/10.1200/JCO.1986.4.9.1326 PMID:3528402
39. Tamoxifen for early breast cancer: An overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 1998; 351(9114):1451-67. https://doi.org/10.1016/S0140-6736(97)11423-4
40. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. The Lancet. 2005; 365(9472):1687-717. https://doi.org/10.1016/S0140-6736(05)66544-0 PMID:15894097
41. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: Suggestions for a new method of treatment, with illustrative cases. Trans Med Chir Soc Edinb. 1896; 15:153-79. https://doi.org/10.1016/S0140-6736(01)72384-7 PMID:29584099
42. Hosford SR, Miller TW. Clinical potential of novel therapeutic targets in breast cancer: CDK4/6, Src, JAK/STAT, PARP, HDAC, and PI3K/AKT/mTOR pathways. Pharmgenomics Pers Med. 2014; 7:203-15. https://doi.org/10.2147/PGPM.S52762 PMID:25206307 PMCID:PMC4157397

43. Newberne JW, Kuhn WL, Elsea JR. Toxicologic studies on clomiphene. Toxicol Appl Pharmacol. 1966; 9(1):44-56. https://doi.org/10.1016/0041-008X(66)90029-9 PMID:5967566
44. Kistner RW. Induction of ovulation with clomiphene citrate (clomid). Obstet Gynecol Surv. 1965; 20(6):873-900. https://doi.org/10.1097/00006254-196512000-00001 PMID:5321936
45. Ring A, Dowsett M. Mechanisms of tamoxifen resistance. Endocr Relat Cancer. 2004; 11(4):643-58. https://doi.org/10.1677/erc.1.00776 PMID:15613444
46. Ali S, Coombes RC. Endocrine-responsive breast cancer and strategies for combating resistance. Nat Rev Cancer. 2002; 2(2):101-12. https://doi.org/10.1038/nrc721 PMID:12635173
47. Kent Osborne C. Mechanisms for tamoxifen resistance in breast cancer: Possible role of tamoxifen metabolism. The Journal of Steroid Biochemistry and Molecular Biology. 1993; 47(1):83-9. https://doi.org/10.1016/0960-0760(93)90060-A PMID:8274445
48. Jordan VC. Fourteenth Gaddum Memorial lecture. A current view of tamoxifen for the treatment and prevention of breast cancer. Br J Pharmacol. 1993; 110(2):507-17. https://doi.org/10.1111/j.1476-5381.1993.tb13840.x PMID:8242225 PMCID:PMC2175926
49. Pollak MN, Huynh HT, Lefebvre SP. Tamoxifen reduces serum insulin-like growth factor I (IGF-I). Breast Cancer Res Treat. 1992; 22(1):91-100. https://doi.org/10.1007/BF01833337 PMID:1421427
50. Derman O, Kanbur NO, Tokur TE. The effect of tamoxifen on sex hormone binding globulin in adolescents with pubertal gynecomastia. J Pediatr Endocrinol Metab. 2004; 17(8):1115-9. https://doi.org/10.1515/JPEM.2004.17.8.1115 PMID:15379424
51. Sakai F, Cheix F, Clavel M, *et al*. Increases in steroid binding globulins induced by tamoxifen in patients with carcinoma of the breast. J Endocrinol. 1978; 76(2):219-26. https://doi.org/10.1677/joe.0.0760219 PMID:564384
52. Radin DP, Patel P. Delineating the molecular mechanisms of tamoxifen's oncolytic actions in estrogen receptor-negative cancers. Eur J Pharmacol. 2016; 781:173-80. https://doi.org/10.1016/j.ejphar.2016.04.017 PMID:27083550
53. Brandt S, Kopp A, Grage B, *et al*. Effects of tamoxifen on transcriptional level of transforming growth factor beta (TGF-beta) isoforms 1 and 2 in tumor tissue during primary treatment of patients with breast cancer. Anticancer Res. 2003; 23(1a):223-9.
54. Skoda AM, Simovic D, Karin V, *et al*. The role of the Hedgehog signaling pathway in cancer: A comprehensive review. Bosn J Basic Med Sci. 2018; 18(1):8-20. https://doi.org/10.17305/bjbms.2018.2756 PMID:29274272 PMCID:PMC5826678
55. Lee W-L, Cheng M-H, Chao H-T, *et al*. The role of selective estrogen receptor modulators on breast cancer: From tamoxifen to raloxifene. Taiwanese Journal of Obstetrics and Gynecology. 2008; 47(1):24-31. https://doi.org/10.1016/S1028-4559(08)60051-0 PMID:18400579
56. Taniguchi-Takizawa T, Kato N, Shimizu M, *et al*. Different substrate elimination rates of model drugs pH-dependently mediated by flavin-containing monooxygenases and cytochromes P450 in human liver microsomes. Drug Metab Pharmacokinet. 2021; 40:100412. https://doi.org/10.1016/j.dmpk.2021.100412 PMID:34352706
57. Cronin-Fenton DP, Damkier P, Lash TL. Metabolism and transport of tamoxifen in relation to its effectiveness: new perspectives on an ongoing controversy. Future Oncol. 2014; 10(1):107-22. https://doi.org/10.2217/fon.13.168 PMID:24328412 PMCID:PMC4319217
58. Wakeling AE, Valcaccia B, Newboult E, *et al*. Non-steroidal antioestrogens--receptor binding and biological response in rat uterus, rat mammary carcinoma and human breast cancer cells. J Steroid Biochem. 1984; 20(1):111-20. https://doi.org/10.1016/0022-4731(84)90197-3 PMID:6538611
59. Colletta AA, Benson JR, Baum M. Alternative mechanisms of action of anti-oestrogens. Breast Cancer Res Treat. 1994; 31(1):5-9. https://doi.org/10.1007/BF00689672 PMID:7981456
60. Schafer JM, Liu H, Bentrem DJ, *et al*. Allosteric silencing of activating function 1 in the 4-hydroxytamoxifen estrogen receptor complex is induced by substituting glycine for aspartate at amino acid 3511. Cancer Research. 2000; 60(18):5097-105.
61. Butta A, MacLennan K, Flanders KC, *et al*. Induction of transforming growth factor beta 1 in human breast cancer *in vivo* following tamoxifen treatment. Cancer Res. 1992; 52(15):4261-4.
62. Ho GH, Ji CY, Phang BH, *et al*. Tamoxifen alters levels of serum insulin-like growth factors and binding proteins in postmenopausal breast cancer patients: a prospective paired cohort study. Ann Surg Oncol. 1998; 5(4):361-7. https://doi.org/10.1007/BF02303501 PMID:9641459
63. Cullen KJ, Lippman ME, Chow D, *et al*. Insulin-like growth factor-II overexpression in MCF-7 cells induces phenotypic changes associated with malignant progression. Mol Endocrinol. 1992; 6(1):91-100. https://doi.org/10.1210/mend.6.1.1310798 PMID:1310798
64. Haran EF, Maretzek AF, Goldberg I, *et al*. Tamoxifen enhances cell death in implanted MCF7 breast cancer by inhibiting endothelium growth. Cancer Res. 1994; 54(21):5511-4.

65. Anzai Y, Holinka CF, Kuramoto H, *et al*. Stimulatory effects of 4-hydroxytamoxifen on proliferation of human endometrial adenocarcinoma cells (Ishikawa line). Cancer Res. 1989; 49(9):2362-5.
66. Condorelli R, Vaz-Luis I. Managing side effects in adjuvant endocrine therapy for breast cancer. Expert Rev Anticancer Ther. 2018; 18(11):1101-12. https://doi.org/10.1080/14737140.2018.1520096 PMID:30188738
67. Osborne CK, Schiff R. Mechanisms of endocrine resistance in breast cancer. Annu Rev Med. 2011; 62:233-47. https://doi.org/10.1146/annurev-med-070909-182917 PMID:20887199 PMCID:PMC3656649
68. Fullwood MJ, Liu MH, Pan YF, *et al*. An oestrogen-receptor-alpha-bound human chromatin interactome. Nature. 2009; 462(7269):58-64. https://doi.org/10.1038/nature08497 PMID:19890323 PMCID:PMC2774924
69. Carroll JS, Liu XS, Brodsky AS, *et al*. Chromosome-wide mapping of estrogen receptor binding reveals long-range regulation requiring the forkhead protein FoxA1. Cell. 2005; 122(1):33-43. https://doi.org/10.1016/j.cell.2005.05.008 PMID:16009131
70. Thomas C, Gustafsson JA. The different roles of ER subtypes in cancer biology and therapy. Nat Rev Cancer. 2011; 11(8):597-608. https://doi.org/10.1038/nrc3093 PMID:21779010
71. Hartman J, Lindberg K, Morani A, *et al*. Estrogen receptor beta inhibits angiogenesis and growth of T47D breast cancer xenografts. Cancer Res. 2006; 66(23):11207-13. https://doi.org/10.1158/0008-5472.CAN-06-0017 PMID:17145865
72. Strom A, Hartman J, Foster JS, *et al*. Estrogen receptor beta inhibits 17beta-estradiol-stimulated proliferation of the breast cancer cell line T47D. Proc Natl Acad Sci U S A. 2004; 101(6):1566-71. https://doi.org/10.1073/pnas.0308319100 PMID:14745018 PMCID:PMC341775
73. Speirs V, Malone C, Walton DS, *et al*. Increased expression of estrogen receptor beta mRNA in tamoxifen-resistant breast cancer patients. Cancer Res. 1999; 59(21):5421-4.
74. Speirs V, Parkes AT, Kerin MJ, *et al*. Coexpression of estrogen receptor alpha and beta: Poor prognostic factors in human breast cancer? Cancer Res. 1999; 59(3):525-8.
75. Taylor SE, Martin-Hirsch PL, Martin FL. Oestrogen receptor splice variants in the pathogenesis of disease. Cancer Lett. 2010; 288(2):133-48. https://doi.org/10.1016/j.canlet.2009.06.017 PMID:19608332
76. Yan Y, Yu L, Castro L, *et al*. ERalpha36, a variant of estrogen receptor alpha, is predominantly localized in mitochondria of human uterine smooth muscle and leiomyoma cells. PLoS One. 2017; 12(10):e0186078. https://doi.org/10.1371/journal.pone.0186078 PMID:29020039 PMCID:PMC5636123
77. Ohe K, Miyajima S, Abe I, *et al*. HMGA1a induces alternative splicing of estrogen receptor alpha in MCF-7 human breast cancer cells. J Steroid Biochem Mol Biol. 2018; 182:21-6. https://doi.org/10.1016/j.jsbmb.2018.04.007 PMID:29678492
78. Shaaban AM, Green AR, Karthik S, *et al*. Nuclear and cytoplasmic expression of ERbeta1, ERbeta2, and ERbeta5 identifies distinct prognostic outcome for breast cancer patients. Clin Cancer Res. 2008; 14(16):5228-35. https://doi.org/10.1158/1078-0432.CCR-07-4528 PMID:18698041
79. Madeira M, Mattar A, Logullo AF, *et al*. Estrogen receptor alpha/beta ratio and estrogen receptor beta as predictors of endocrine therapy responsiveness-a randomized neoadjuvant trial comparison between anastrozole and tamoxifen for the treatment of postmenopausal breast cancer. BMC Cancer. 2013; 13:425. https://doi.org/10.1186/1471-2407-13-425 PMID:24047421 PMCID:PMC3851532
80. Guillette TC, Jackson TW, Belcher SM. Duality of estrogen receptor beta action in cancer progression. Curr Opin Pharmacol. 2018; 41:66-73. https://doi.org/10.1016/j.coph.2018.05.001 PMID:29772419 PMCID:PMC8008732
81. Kelly MJ, Levin ER. Rapid actions of plasma membrane estrogen receptors. Trends Endocrinol Metab. 2001; 12(4):152-6. https://doi.org/10.1016/S1043-2760(01)00377-0 PMID:11295570
82. Levin ER, Pietras RJ. Estrogen receptors outside the nucleus in breast cancer. Breast Cancer Res Treat. 2008; 108(3):351-61. https://doi.org/10.1007/s10549-007-9618-4 PMID:17592774
83. Fan P, Wang J, Santen RJ, *et al*. Long-term treatment with tamoxifen facilitates translocation of estrogen receptor alpha out of the nucleus and enhances its interaction with EGFR in MCF-7 breast cancer cells. Cancer Res. 2007; 67(3):1352-60. https://doi.org/10.1158/0008-5472.CAN-06-1020 PMID:17283173
84. Tonetti DA, Jordan VC. The role of estrogen receptor mutations in tamoxifen-stimulated breast cancer. J Steroid Biochem Mol Biol. 1997; 62(2-3):119-28. https://doi.org/10.1016/S0960-0760(97)00034-4 PMID:9393947
85. Alluri PG, Speers C, Chinnaiyan AM. Estrogen receptor mutations and their role in breast cancer progression. Breast Cancer Res. 2014; 16(6):494. https://doi.org/10.1186/s13058-014-0494-7 PMID:25928204 PMCID:PMC4429420
86. Clusan L, Le Goff P, Flouriot G, *et al*. A Closer Look at Estrogen receptor mutations in breast cancer and their implications for estrogen and antiestrogen responses. Int J Mol Sci. 2021; 22(2). https://doi.org/10.3390/ijms22020756 PMID:33451133 PMCID:PMC7828590

87. Altwegg KA, Vadlamudi RK. Role of estrogen receptor coregulators in endocrine resistant breast cancer. Explor Target Antitumor Ther. 2021; 2:385-400. https://doi.org/10.37349/etat.2021.00052 PMID:34528025 PMCID:PMC8439438
88. Shiau AK, Barstad D, Loria PM, *et al*. The structural basis of estrogen receptor/coactivator recognition and the antagonism of this interaction by tamoxifen. Cell. 1998; 95(7):927-37. https://doi.org/10.1016/S0092-8674(00)81717-1 PMID:9875847
89. Haque MM, Desai KV. Pathways to endocrine therapy resistance in breast cancer. Front Endocrinol (Lausanne). 2019; 10:573. https://doi.org/10.3389/fendo.2019.00573 PMID:31496995 PMCID:PMC6712962
90. Weiner M, Skoog L, Fornander T, *et al*. Oestrogen receptor co-activator AIB1 is a marker of tamoxifen benefit in postmenopausal breast cancer. Ann Oncol. 2013; 24(8):1994-9. https://doi.org/10.1093/annonc/mdt159 PMID:23670096 PMCID:PMC3718507
91. Lavinsky RM, Jepsen K, Heinzel T, *et al*. Diverse signaling pathways modulate nuclear receptor recruitment of N-CoR and SMRT complexes. Proc Natl Acad Sci U S A. 1998; 95(6):2920-5. https://doi.org/10.1073/pnas.95.6.2920 PMID:9501191 PMCID:PMC19670
92. Ranganathan P, Nadig N, Nambiar S. Non-canonical estrogen signaling in endocrine resistance. Frontiers in Endocrinology. 2019; 10. https://doi.org/10.3389/fendo.2019.00708 PMID:31749762 PMCID:PMC6843063
93. Schiff R, Reddy P, Ahotupa M, *et al*. Oxidative stress and AP-1 activity in tamoxifen-resistant breast tumors *in vivo.* J Natl Cancer Inst. 2000; 92(23):1926-34. https://doi.org/10.1093/jnci/92.23.1926 PMID:11106684
94. Johnston SR, Lu B, Scott GK, *et al*. Increased activator protein-1 DNA binding and c-Jun NH2-terminal kinase activity in human breast tumors with acquired tamoxifen resistance. Clin Cancer Res. 1999; 5(2):251-6.
95. Jeselsohn R, Cornwell M, Pun M, *et al*. Embryonic transcription factor SOX9 drives breast cancer endocrine resistance. Proc Natl Acad Sci U S A. 2017; 114(22):E4482-E91. https://doi.org/10.1073/pnas.1620993114 PMID:28507152 PMCID:PMC5465894
96. Hurtado A, Holmes KA, Ross-Innes CS, *et al*. FOXA1 is a key determinant of estrogen receptor function and endocrine response. Nat Genet. 2011; 43(1):27-33. https://doi.org/10.1038/ng.730 PMID:21151129 PMCID:PMC3024537
97. Robinson JL, Carroll JS. FoxA1 is a key mediator of hormonal response in breast and prostate cancer. Front Endocrinol (Lausanne). 2012; 3:68. https://doi.org/10.3389/fendo.2012.00068 PMID:22649425 PMCID:PMC3355944
98. Magnani L, Stoeck A, Zhang X, *et al*. Genome-wide reprogramming of the chromatin landscape underlies endocrine therapy resistance in breast cancer. Proc Natl Acad Sci U S A. 2013; 110(16):E1490-9. https://doi.org/10.1073/pnas.1219992110 PMID:23576735 PMCID:PMC3631697
99. Yun J, Pannuti A, Espinoza I, *et al*. Crosstalk between PKCalpha and Notch-4 in endocrine-resistant breast cancer cells. Oncogenesis. 2013; 2:e60. https://doi.org/10.1038/oncsis.2013.26 PMID:23917222 PMCID:PMC3759125
100. Kalyanaraman A, Gnanasampanthapandian D, Shanmughan P, *et al*. Tamoxifen induces stem-like phenotypes and multidrug resistance by altering epigenetic regulators in ERalpha+ breast cancer cells. Stem Cell Investig. 2020; 7:20. https://doi.org/10.21037/sci-2020-020 PMID:33294429 PMCID:PMC7715663
101. Nicholson RI, Hutcheson IR, Jones HE, *et al*. Growth factor signalling in endocrine and anti-growth factor resistant breast cancer. Rev Endocr Metab Disord. 2007; 8(3):241-53. https://doi.org/10.1007/s11154-007-9033-5 PMID:17486454
102. Knowlden JM, Hutcheson IR, Barrow D, *et al*. Insulin-like growth factor-I receptor signaling in tamoxifen-resistant breast cancer: a supporting role to the epidermal growth factor receptor. Endocrinology. 2005; 146(11):4609-18. https://doi.org/10.1210/en.2005-0247 PMID:16037379
103. Giuliano M, Trivedi MV, Schiff R. Bidirectional Crosstalk between the Estrogen Receptor and Human Epidermal Growth Factor Receptor 2 Signaling Pathways in Breast Cancer: Molecular Basis and Clinical Implications. Breast Care (Basel). 2013; 8(4):256-62. https://doi.org/10.1159/000354253 PMID:24415978 PMCID:PMC3808214
104. Hasson SP, Rubinek T, Ryvo L, et al. Endocrine resistance in breast cancer: focus on the phosphatidylinositol 3-kinase/akt/mammalian target of rapamycin signaling pathway. Breast Care (Basel). 2013; 8(4):248-55. https://doi.org/10.1159/000354757 PMID:24415977 PMCID:PMC3808218
105. Benz CC, Scott GK, Sarup JC, *et al*. Estrogen-dependent, tamoxifen-resistant tumorigenic growth of MCF-7 cells transfected with HER2/neu. Breast Cancer Res Treat. 1992; 24(2):85-95. https://doi.org/10.1007/BF01961241 PMID:8095168
106. Chung YL, Sheu ML, Yang SC, *et al*. Resistance to tamoxifen-induced apoptosis is associated with direct interaction between Her2/neu and cell membrane estrogen receptor in breast cancer. Int J Cancer. 2002; 97(3):306-12. https://doi.org/10.1002/ijc.1614 PMID:11774281
107. He H, Sinha I, Fan R, *et al*. c-Jun/AP-1 overexpression reprograms ERalpha signaling related to tamoxifen response in ERalpha-positive breast cancer. Oncogene. 2018;37(19):2586-600. https://doi.org/10.1038/s41388-018-0165-8 PMID:29467493
108. Sasser AK, Sullivan NJ, Studebaker AW, *et al*. Interleukin-6 is a potent growth factor for ER-alpha-positive human breast cancer. FASEB J. 2007; 21(13):3763-70. https://doi.org/10.1096/fj.07-8832com PMID:17586727

109. Gottardis MM, Ricchio ME, Satyaswaroop PG, *et al*. Effect of steroidal and nonsteroidal antiestrogens on the growth of a tamoxifen-stimulated human endometrial carcinoma (EnCa101) in athymic mice. Cancer Res. 1990; 50(11):3189-92.
110. Han XL, Liehr JG. Induction of covalent DNA adducts in rodents by tamoxifen. Cancer Res. 1992; 52(5):1360-3.
111. Arpino G, Green SJ, Allred DC, *et al*. HER-2 amplification, HER-1 expression, and tamoxifen response in estrogen receptor-positive metastatic breast cancer: A southwest oncology group study. Clin Cancer Res. 2004; 10(17):5670-6. https://doi.org/10.1158/1078-0432.CCR-04-0110 PMID:15355892
112. Gee JM, Robertson JF, Gutteridge E, *et al*. Epidermal growth factor receptor/HER2/insulin-like growth factor receptor signalling and oestrogen receptor activity in clinical breast cancer. Endocr Relat Cancer. 2005; 12 Suppl 1:S99-S111. https://doi.org/10.1677/erc.1.01005 PMID:16113104
113. Dowsett M, Johnston S, Martin LA, *et al*. Growth factor signalling and response to endocrine therapy: the Royal Marsden Experience. Endocr Relat Cancer. 2005; 12 Suppl 1:S113-7. https://doi.org/10.1677/erc.1.01044 PMID:16113087
114. Gutierrez MC, Detre S, Johnston S, *et al*. Molecular changes in tamoxifen-resistant breast cancer: Relationship between estrogen receptor, HER-2, and p38 mitogen-activated protein kinase. J Clin Oncol. 2005; 23(11):2469-76. https://doi.org/10.1200/JCO.2005.01.172 PMID:15753463
115. Kirkegaard T, Witton CJ, McGlynn LM, *et al*. AKT activation predicts outcome in breast cancer patients treated with tamoxifen. J Pathol. 2005; 207(2):139-46. https://doi.org/10.1002/path.1829 PMID:16088978
116. Fex G, Adielsson G, Mattson W. Oestrogen-like effects of tamoxifen on the concentration of proteins in plasma. Acta Endocrinol (Copenh). 1981; 97(1):109-13. https://doi.org/10.1530/acta.0.0970109 PMID:6784425
117. Jordan VC, Fritz NF, Tormey DC. Endocrine effects of adjuvant chemotherapy and long-term tamoxifen administration on node-positive patients with breast cancer. Cancer Res. 1987; 47(2):624-30.
118. Ferrazzi E, Cartei G, Mattarazzo R, et al. Oestrogen-like effect of tamoxifen on vaginal epithelium. Br Med J. 1977; 1(6072):1351-2. https://doi.org/10.1136/bmj.1.6072.1351-e PMID:861624 PMCID:PMC1607200
119. Murphy LC, Sutherland RL. A high-affinity binding site for the antioestrogens, tamoxifen and CI 628, in immature rat uterine cytosol which is distinct from the oestrogen receptor. J Endocrinol. 1981; 91(1):155-61. https://doi.org/10.1677/joe.0.0910155 PMID:7028904
120. Sudo K, Monsma FJ, Jr., Katzenellenbogen BS. Antiestrogen-binding sites distinct from the estrogen receptor: Subecellular localization, ligand specificity, and distribution in tissues of the rat. Endocrinology. 1983; 112(2):425-34. https://doi.org/10.1210/endo-112-2-425 PMID:6848356
121. Miller MA, Katzenellenbogen BS. Characterization and quantitation of antiestrogen binding sites in estrogen receptor-positive and -negative human breast cancer cell lines. Cancer Res. 1983; 43(7):3094-100.
122. Katzenellenbogen BS, Miller MA, Mullick A, *et al*. Antiestrogen action in breast cancer cells: modulation of proliferation and protein synthesis, and interaction with estrogen receptors and additional antiestrogen binding sites. Breast Cancer Res Treat. 1985; 5(3):231-43. https://doi.org/10.1007/BF01806018 PMID:4027393
123. O'Brian CA, Liskamp RM, Solomon DH, *et al*. Inhibition of protein kinase C by tamoxifen. Cancer Res. 1985; 45(6):2462-5.
124. Lam HY. Tamoxifen is a calmodulin antagonist in the activation of cAMP phosphodiesterase. Biochem Biophys Res Commun. 1984; 118(1):27-32. https://doi.org/10.1016/0006-291X(84)91062-3 PMID:6320825
125. Brandes LJ, Macdonald LM, Bogdanovic RP. Evidence that the antiestrogen binding site is a histamine or histamine-like receptor. Biochem Biophys Res Commun. 1985; 126(2):905-10. https://doi.org/10.1016/0006-291X(85)90271-2 PMID:2858205
126. Hiemke C, Ghraf R. Interaction of non-steroidal antiestrogens with dopamine receptor binding. J Steroid Biochem. 1984; 21(6):663-7. https://doi.org/10.1016/0022-4731(84)90028-1 PMID:6098784
127. Ben-Baruch G, Schreiber G, Sokolovsky M. Cooperativity pattern in the interaction of the antiestrogen drug clomiphene with the Muscarinic receptors. Mol Pharmacol. 1982; 21(2):287-93.
128. Saji S, Hirose M, Toi M. Clinical significance of estrogen receptor beta in breast cancer. Cancer Chemother Pharmacol. 2005; 56 Suppl 1:21-6. https://doi.org/10.1007/s00280-005-0107-3 PMID:16273360
129. Murphy LC, Watson PH. Is oestrogen receptor-beta a predictor of endocrine therapy responsiveness in human breast cancer? Endocr Relat Cancer. 2006; 13(2):327-34. https://doi.org/10.1677/erc.1.01141 PMID:16728566
130. Matthews J, Wihlen B, Tujague M, *et al*. Estrogen Receptor (ER) beta modulates ERalpha-mediated transcriptional activation by altering the recruitment of c-Fos and c-Jun to estrogen-responsive promoters. Mol Endocrinol. 2006; 20(3):534-43. https://doi.org/10.1210/me.2005-0140 PMID:16293641
131. Stossi F, Barnett DH, Frasor J, *et al*. Transcriptional profiling of estrogen-regulated gene expression via Estrogen Receptor (ER) alpha or ERbeta in human osteosarcoma cells: distinct and common target genes for these receptors. Endocrinology. 2004; 145(7):3473-86. https://doi.org/10.1210/en.2003-1682 PMID:15033914

132. Chang EC, Frasor J, Komm B, *et al*. Impact of estrogen receptor beta on gene networks regulated by estrogen receptor alpha in breast cancer cells. Endocrinology. 2006; 147(10):4831-42. https://doi.org/10.1210/en.2006-0563 PMID:16809442
133. Wang X, Zhang H, Chen X. Drug resistance and combating drug resistance in cancer. Cancer Drug Resist. 2019; 2:141-60. https://doi.org/10.20517/cdr.2019.10 PMID:34322663 PMCID:PMC8315569
134. Vaidya FU, Sufiyan Chhipa A, Mishra V, *et al*. Molecular and cellular paradigms of multidrug resistance in cancer. Cancer Rep (Hoboken). 2020 :e1291. https://doi.org/10.1002/cnr2.1291 PMID:33052041 PMCID:PMC9780431
135. Bekele RT, Venkatraman G, Liu RZ, et al. Oxidative stress contributes to the tamoxifen-induced killing of breast cancer cells: Implications for tamoxifen therapy and resistance. Sci Rep. 2016; 6:21164. https://doi.org/10.1038/srep21164 PMID:26883574 PMCID:PMC4756695
136. Mansoori B, Mohammadi A, Davudian S, et al. The Different Mechanisms of Cancer Drug Resistance: A Brief Review. Adv Pharm Bull. 2017; 7(3):339-48. https://doi.org/10.15171/apb.2017.041 PMID:29071215 PMCID:PMC5651054
137. Bekele RT, Venkatraman G, Liu RZ, I. Oxidative stress contributes to the tamoxifen-induced killing of breast cancer cells: Implications for tamoxifen therapy and resistance. Sci Rep. 2016; 6:21164. https://doi.org/10.1038/srep21164 PMID:26883574 PMCID:PMC4756695
138. Liu Y, Li Q, Zhou L, et al. Cancer drug resistance: redox resetting renders a way. Oncotarget. 2016; 7(27):42740-61. https://doi.org/10.18632/oncotarget.8600 PMID:27057637 PMCID:PMC5173169
139. Choi HK, Yang JW, Roh SH, *et al*. Induction of multidrug resistance associated protein 2 in tamoxifen-resistant breast cancer cells. Endocr Relat Cancer. 2007; 14(2):293-303. https://doi.org/10.1677/ERC-06-0016 PMID:17639045
140. Kathawala RJ, Gupta P, Ashby CR, Jr., *et al*. The modulation of ABC transporter-mediated multidrug resistance in cancer: A review of the past decade. Drug Resist Updat. 2015; 18:1-17. https://doi.org/10.1016/j.drup.2014.11.002 PMID:25554624
141. Wilkens S. Structure and mechanism of ABC transporters. F1000Prime Rep. 2015; 7:14. https://doi.org/10.12703/P7-14 PMID:25750732 PMCID:PMC4338842
142. Dean M, Rzhetsky A, Allikmets R. The human ATP-Binding Cassette (ABC) transporter superfamily. Genome Res. 2001; 11(7):1156-66. https://doi.org/10.1101/gr.184901 PMID:11435397
143. Theile D, Wizgall P. Acquired ABC-transporter overexpression in cancer cells: transcriptional induction or Darwinian selection? Naunyn Schmiedebergs Arch Pharmacol. 2021; 394(8):1621-32. https://doi.org/10.1007/s00210-021-02112-3 PMID:34236499 PMCID:PMC8298356
144. Xue X, Liang XJ. Overcoming drug efflux-based multidrug resistance in cancer with nanotechnology. Chin J Cancer. 2012; 31(2):100-9. https://doi.org/10.5732/cjc.011.10326 PMID:22237039 PMCID:PMC3777470
145. Lu JF, Pokharel D, Bebawy M. MRP1 and its role in anticancer drug resistance. Drug Metab Rev. 2015; 47(4):406-19. https://doi.org/10.3109/03602532.2015.1105253 PMID:26541366
146. The UniProt C. UniProt: The universal protein knowledgebase. Nucleic Acids Res. 2017; 45(D1):D158-D69. https://doi.org/10.1093/nar/gkw1099 PMID:27899622 PMCID:PMC5210571
147. Liu W, Xie Y, Ma J, et al. IBS: An illustrator for the presentation and visualization of biological sequences. Bioinformatics. 2015; 31(20):3359-61. https://doi.org/10.1093/bioinformatics/btv362 PMID:26069263 PMCID:PMC4595897
148. Wang X, Li Y, Qian Y, et al. Extracellular ATP, as an energy and phosphorylating molecule, induces different types of drug resistances in cancer cells through ATP internalization and intracellular ATP level increase. Oncotarget. 2017; 8(50):87860-77. https://doi.org/10.18632/oncotarget.21231 PMID:29152126 PMCID:PMC5675678
149. Schneider V, Krieger ML, Bendas G, *et al*. Contribution of intracellular ATP to cisplatin resistance of tumor cells. J Biol Inorg Chem. 2013; 18(2):165-74. https://doi.org/10.1007/s00775-012-0960-6 PMID:23183891
150. Qian Y, Wang X, Liu Y, *et al*. Extracellular ATP is internalized by macropinocytosis and induces intracellular ATP increase and drug resistance in cancer cells. Cancer Lett. 2014; 351(2):242-51. https://doi.org/10.1016/j.canlet.2014.06.008 PMID:24973521
151. Yin Y, Li W, Deng M, *et al*. Extracellular high mobility group box chromosomal protein 1 promotes drug resistance by increasing the expression of Pglycoprotein expression in gastric adenocarcinoma cells. Mol Med Rep. 2014; 9(4):1439-43. https://doi.org/10.3892/mmr.2014.1961 PMID:24549588
152. Callaghan R, Higgins CF. Interaction of tamoxifen with the multidrug resistance P-glycoprotein. Br J Cancer. 1995; 71(2):294-9. https://doi.org/10.1038/bjc.1995.59 PMID:7841043 PMCID:PMC2033580
153. Wilting RH, Dannenberg JH. Epigenetic mechanisms in tumorigenesis, tumor cell heterogeneity and drug resistance. Drug Resist Updat. 2012; 15(1-2):21-38. https://doi.org/10.1016/j.drup.2012.01.008 PMID:22356866
154. Berdasco M, Esteller M. Clinical epigenetics: Seizing opportunities for translation. Nat Rev Genet. 2019; 20(2):109-27. https://doi.org/10.1038/s41576-018-0074-2 PMID:30479381

155. Garcia-Martinez L, Zhang Y, Nakata Y, et al. Epigenetic mechanisms in breast cancer therapy and resistance. Nat Commun. 2021; 12(1):1786. https://doi.org/10.1038/s41467-021-22024-3 PMID:33741974 PMCID:PMC7979820
156. Zeller C, Brown R. Therapeutic modulation of epigenetic drivers of drug resistance in ovarian cancer. Ther Adv Med Oncol. 2010; 2(5):319-29. https://doi.org/10.1177/1758834010375759 PMID:21789144 PMCID:PMC3126026
157. Glasspool RM, Teodoridis JM, Brown R. Epigenetics as a mechanism driving polygenic clinical drug resistance. Br J Cancer. 2006; 94(8):1087-92. https://doi.org/10.1038/sj.bjc.6603024 PMID:16495912 PMCID:PMC2361257
158. Teodoridis JM, Strathdee G, Brown R. Epigenetic silencing mediated by CpG island methylation: potential as a therapeutic target and as a biomarker. Drug Resist Updat. 2004; 7(4-5):267-78. https://doi.org/10.1016/j.drup.2004.06.005 PMID:15533764
159. Martin HL, Smith L, Tomlinson DC. Multidrug-resistant breast cancer: current perspectives. Breast Cancer (Dove Med Press). 2014; 6:1-13. https://doi.org/10.2147/BCTT.S37638 PMID:24648765 PMCID:PMC3929252
160. Watanabe T, Oba T, Tanimoto K, et al. Tamoxifen resistance alters sensitivity to 5-fluorouracil in a subset of estrogen receptor-positive breast cancer. PLoS One. 2021; 16(6):e0252822. https://doi.org/10.1371/journal.pone.0252822 PMID:34101751 PMCID:PMC8186817
161. Behbahani GD, Khani S, Hosseini HM, *et al*. The role of exosomes contents on genetic and epigenetic alterations of recipient cancer cells. Iran J Basic Med Sci. 2016; 19(10):1031-9.
162. Qian Z, Shen Q, Yang X, et al. The role of extracellular vesicles: An epigenetic view of the cancer microenvironment. Biomed Res Int. 2015; 2015:649161. https://doi.org/10.1155/2015/649161 PMID:26582468 PMCID:PMC4637039
163. Guo QR, Wang H, Yan YD, et al. The role of exosomal microRNA in cancer drug resistance. Front Oncol. 2020;10:472. https://doi.org/10.3389/fonc.2020.00472 PMID:32318350 PMCID:PMC7154138
164. Johnson AB, O'Malley BW. Steroid receptor coactivators 1, 2, and 3: Critical regulators of nuclear receptor activity and Steroid Receptor Modulator (SRM)-based cancer therapy. Mol Cell Endocrinol. 2012; 348(2):430-9. https://doi.org/10.1016/j.mce.2011.04.021 PMID:21664237 PMCID:PMC3202666
165. Murakami S, Nagari A, Kraus WL. Dynamic assembly and activation of estrogen receptor alpha enhancers through coregulator switching. Genes Dev. 2017; 31(15):1535-48. https://doi.org/10.1101/gad.302182.117 PMID:28887413 PMCID:PMC5630019
166. Yi P, Wang Z, Feng Q, et al. Structure of a biologically active estrogen receptor-coactivator complex on DNA. Mol Cell. 2015; 57(6):1047-58. https://doi.org/10.1016/j.molcel.2015.01.025 PMID:25728767 PMCID:PMC4369429
167. Li W, Notani D, Ma Q, et al. Functional roles of enhancer RNAs for oestrogen-dependent transcriptional activation. Nature. 2013; 498(7455):516-20. https://doi.org/10.1038/nature12210 PMID:23728302 PMCID:PMC3718886
168. Fan S, Wang J, Yuan R, *et al*. BRCA1 inhibition of estrogen receptor signaling in transfected cells. Science. 1999; 284(5418):1354-6. https://doi.org/10.1126/science.284.5418.1354 PMID:10334989
169. Jozwik KM, Carroll JS. Pioneer factors in hormone-dependent cancers. Nat Rev Cancer. 2012; 12(6):381-5. https://doi.org/10.1038/nrc3263 PMID:22555282
170. He J, Feng C, Zhu H, *et al*. Grainyhead-like 2 as a double-edged sword in development and cancer. Am J Transl Res. 2020; 12(2):310-31.
171. Chi D, Singhal H, Li L, et al. Estrogen receptor signaling is reprogrammed during breast tumorigenesis. Proc Natl Acad Sci U S A. 2019; 116(23):11437-43. https://doi.org/10.1073/pnas.1819155116 PMID:31110002 PMCID:PMC6561257
172. Zhou W, Slingerland JM. Links between oestrogen receptor activation and proteolysis: Relevance to hormone-regulated cancer therapy. Nat Rev Cancer. 2014; 14(1):26-38. https://doi.org/10.1038/nrc3622 PMID:24505618
173. Teyssier C, Le Romancer M, Sentis S, *et al*. Protein arginine methylation in estrogen signaling and estrogen-related cancers. Trends Endocrinol Metab. 2010; 21(3):181-9. https://doi.org/10.1016/j.tem.2009.11.002 PMID:20005732
174. Manavathi B, Samanthapudi VS, Gajulapalli VN. Estrogen receptor coregulators and pioneer factors: The orchestrators of mammary gland cell fate and development. Front Cell Dev Biol. 2014; 2:34. https://doi.org/10.3389/fcell.2014.00034 PMID:25364741 PMCID:PMC4207046
175. Holding AN, Giorgi FM, Donnelly A, et al. Correction to: VULCAN integrates ChIP-seq with patient-derived co-expression networks to identify GRHL2 as a key co-regulator of ERa at enhancers in breast cancer. Genome Biol. 2019; 20(1):122. https://doi.org/10.1186/s13059-019-1733-0 PMID:31200751 PMCID:PMC6567503
176. Chan HL, Morey L. Emerging Roles for Polycomb-Group Proteins in Stem Cells and Cancer. Trends Biochem Sci. 2019; 44(8):688-700. https://doi.org/10.1016/j.tibs.2019.04.005 PMID:31085088
177. Shi B, Liang J, Yang X, et al. Integration of estrogen and Wnt signaling circuits by the polycomb group protein EZH2 in breast cancer cells. Mol Cell Biol. 2007; 27(14):5105-19. https://doi.org/10.1128/MCB.00162-07 PMID:17502350 PMCID:PMC1951944
178. Lee JY, Won HY, Park JH, et al. MEL-18 loss mediates estrogen receptor-alpha downregulation and hormone independence. J Clin Invest. 2015; 125(5):1801-14. https://doi.org/10.1172/JCI73743 PMID:25822021 PMCID:PMC4463188