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ORIGINAL RESEARCH

Action of Estrogen in Breast Cancer: A review Study

Suad Lateef Ibrahim [1], Rachel Berkson [2]

[1] *Faculty of Pharmacy, University of Kufa, Iraq.*
[2] *Wellcome Sanger Institute, 215 Euston Road, London, UK.*

CORRESPONDING AUTHOR

Suad Lateef Ibrahim,
Faculty of Pharmacy,
University of Kufa, Iraq.
Email:
suadl.ibrahim@uokufa.edu.iq

ABSTRACT

Estrogen hormone is one of the steroid hormones has a critical role in breast cancer etiology. It has been implicated in proliferation and differentiation of cells through its action promoting binding of its receptor to DNA, changing transcriptional expression of target genes. In addition to the classical DNA binding mechanism, estrogen can also regulate gene expression through a no genomic mechanism associated with activation a variety of signal transduction pathways (e.g. PI3`K/AKT, ERK/MAPK, PLC/PKCs , p38/MAPK). Dysregulation of the balance between pro-apoptotic and anti-apoptotic members of the Bcl-2 family, would result in apoptosis inhibition and tumor genesis (Chimento et al., 2022). Also, poor responses towards hormonal therapy, radiotherapy, and chemotherapy and treatment resistance are likely caused by dysregulation of apoptosis. Importantly, E2 has been shown to prevent apoptosis, first through its action in activation of anti-apoptotic proteins like Bcl-xl and Bcl-2 in breast cells like MCF-7, T47D and ZR-75-1 or due to its metabolites independently of ER. Estrogen metabolism includes several very important pathways that can possibly induce de novo DNA mutation. These pathways include:2, &4-hydroxylation, 16 α hydroxylation and 4 hydroxyestradiol-quinone-adenine/guanine adduct depurination, which subsequently participate in DNA damage that can lead to breast cancer. Endocrine resistance is considered one of the most permanent problems that can reduce the benefits of breast cancer treatment. Alteration of microRNAs expression, polymorphisms occurring in tamoxifen metabolism, and using redundant alternative signaling pathways, resulting in poor treatment responses of breast cancer patients and induction of endocrine resistance. Thus, most proposed therapeutic strategies will be based on a combination of drugs targeting various pathways alongside endocrine therapy that may improve the outcomes of endocrine responses in resistant breast cancer cells.

Keywords: breast cancer, ER receptors, estrogen metabolism, endocrine resistance.

1. INTRODUCTION

Estrogen hormone is one of the steroid hormones with a vital role in the etiology of breast cancer. Estrogen has been implicated in proliferation and differentiation of cells through its action promoting binding of its receptor to DNA, changing transcriptional expression of target genes. Estrogen's action is mediated through binding to intracellular receptors which belong to the nuclear receptor family, which exist in two isoforms, ERα and ERβ. These two isoforms are characterized by the existence of five domains, as seen in figure 1, which include A/B or AF-1, which is present at the N-terminal and responsible for transactivation. Second, the C domain, also called the DNA-binding domain (DBD), usually binds to estrogen response elements in DNA. The D domain represents a hinge region and functions to connect the C and E domains. Finally, the E domain at the C-terminal contains binding sites for coactivator and corepressor proteins and also has the ligand binding cavity. In the presence of ligand, the E-domain is capable of inducing gene transcription. Alternatively, the A/B domain is responsible for tansactivating gene transcription in the absence of estrogen hormone (Millas, I., & Duarte Barros, M. 2021).

Additionally, the two ER isoforms have an important region consisting of activation functions (AFs), which are AF-1 and AF-2, that are capable of interaction with transcription cofactors to induce gene transcription. So, gene expression is mediated by direct binding of ERα to estrogen response elements within the promoters of estrogen-regulated genes or through ERα recruitment to DNA by interaction with transcription cofactors that might result in either activation or repression of gene transcription. ERα - ligand dependent transcription activity is mediated by activation of the activation function-1 (AF-1) domain and the hormone dependent AF-2 , while ERβ has no functional AF-1 domain (Johansson et al., 2021; Millas and Duarte Barros, 2021).

Estrogen influences cellular changes by numerous mechanisms. First, estrogen binding to its receptors activates a conformational change in ER promoting dimerization and binding to estrogen response elements ERE. ER-ligand binds directly to the ERE or indirectly by protein –protein interactions with activator proteins 1 such as SP1 and AP 1, which are found at promoters of estrogen responsive genes. In either case, this interaction would result in recruitment of co-regulator proteins to the promoter of the target genes and induction of transcriptional activity. These co-regulator proteins include co-activators such as p160/SRC, a member of the Steroid Receptor Coactivator family, SRC1/NcoA1(Nuclear Receptor Coactivators), p300, CBP(CREB - Binding Protein), and corepressors like MTA1 (Metastasis associated-1) and NcoR (Nuclear Receptor Co-repressor (Jafari and Hussain, 2022; Reddy, McCarthy and Raval, 2022; and Barreto, Mcgovern and Garcia-segura, 2021). In addition, the role of estrogen in cell proliferation can be explained by its effect on stimulation of induction of G1-to S-phase transition, enabling of activation of c-myc which regulates cyclin D expression with retinoblastoma protein phosphorylation and cyclin-dependent kinase activation (CDK) (Chimento et al., 2022).

In addition to the classical DNA binding mechanism, estrogen can also regulate gene expression through a nongenomic mechanism associated with activation a variety of signal transduction pathways (e.g. PI3`K/AKT, ERK/MAPK, PLC/PKCs , p38/MAPK) (Barreto et al., 2021).

Figure (1): A simple diagram of the estrogen receptor adapted from (Uversky, 2020). The figure explains the functional ER domains which include the DNA-binding domain (DBD), the ligand-binding domain (LBD), the ligand-dependent activation function AF-2 and the ligand independent activation function AF-1.

2. Role of Estrogen and ER signaling pathway in breast cancer

Numerous signaling pathways are activated upon estrogens binding to their plasma membrane receptors (extra-nuclear signaling). For instance, E2-ERα has been implicated in activation of the IGF-1 receptor that possibly leads to activation of the MAPK signaling pathway Also, activation of ERα by estrogen activates the epidermal growth factor (EGF) receptor which depends on activation of Src kinase, G proteins and metalloproteinases that ultimately promote MAPK kinase (Barreto, Mcgovern and Garcia-segura, 2021; Fuentes and Silveyra, 2019; Theocharis and Karamanos, 2019 & Solar Fernandez et al., 2021). In addition, this protein kinase can phosphorylate target transcription factors, such as STATs, AP-1 or EIK-1, resulting in increased transcription activity. For instance, the c-fos gene is activated by enhanced AP-1 transcription activity through E2- mediated MAPK activation (Barreto, Mcgovern and Garcia-segura, 2021).

Additionally, activated protein kinases can modulate the function of ERs, enabling the classical action of ER. For instance, Jeffreys et al., 2020 demonstrated the phosphorylation of ERα at specific sites like serine 104, serine 106 and serine 118 in the AF-1 domain, which following activation by the MAPK signaling pathway, associates with increasing ERα activity in a ligand independent manner. ERα hyperactivity may contribute to endocrine therapy resistance in breast cancer. (Jeffreys et al., 2020). These studies suggested that tamoxifen, which is an example of a selective estrogen receptor modulator (SERM) and one of the anti-estrogen therapeutic agents, works by inhibiting classical ER-target genes in ERpositive breast cancer.

Aside from estrogen inducing MAPK, the PI3`K signaling pathway can also be activated by signaling from E2-induced membrane ER, which can subsequently enhance transcription of hundreds of target genes, such as cyclin D. Cyclin D genes have an important role in cell progression by promoting the G1 to S phase progression of the cell cycle. It is believed that Cyclin D gene activation results from ERα –activated by estrogen interacting with the p85 regulatory unit of PI3`K and Src kinase. A PI3`K inhibitor caused inhibition in transcription activity of the related genes (Barreto, Mcgovern and Garcia-segura, 2021). Also, activation of ERα by estrogen activates the epidermal growth factor (EGF) receptor which depends on activation of Src kinase, G proteins and metalloproteinases, and can result in promoting PI3`K/Akt kinase signaling. In addition, activation of PI3`K by estrogen can be mediated through IGF-IR/ insulin receptor by interaction with p85 (Shrihastini et al., 2021).

More importantly, this activated protein kinase, PI3`K will lead to phosphorylation and activation of transcriptional factors, resulting in regulation of gene expression. For example, the transcription factor, nuclear factors NF-kB are phosphorylated following

activation of the PI3`K/Akt kinase by E2, and then this NF-kB phosphorylation leads to increased expression of genes that contain NF-kB response elements.The NF-kB may be a target for phosphorylation by AKT kinases (Barreto, Mcgovern and Garcia-segura, 2021). Thus , PI3`K signaling activates AKT and NF-kB signaling, causing cell survival (apoptosis inhibition) (Escher et al., 2021). Furthermore, a high interdependence between PI3`K and ER signaling pathways may be also involved in activation of the estrogen independent-ER pathway via PI3`K/ AKT/ mTOR, resulting in enhanced cellular proliferation in absence of the estrogen. This pathway is postulated to be mediated by phosphorylation of ERα at serine 167, either by S6K1 1, a downstream effecter of mTOR, or by AKT (Shrihastini et al., 2021). Importantly, the mechanism by which PI3`K promotes the estrogen independent pathway can be prevented by aromatase inhibitors, an inhibitor of estrogen synthesis. This finding was supported by (Ledda et al., 2021, Fan and Jordan, 2022), who reported that regulation of breast cancer proliferation can be achieved through the potential therapeutics based on reducing ERα levels or blocking estrogen synthesis or inhibiting estrogen binding to ERα in ERα positive MCF-7 breast cells, (Ledda et al., 2021, Dong et al., 2021, Fan and Jordan, 2022).

On the other hand, over-activation of the PI3`K pathway may confer breast cancer resistance to endocrine therapy (Shrihastini et al., 2021 & Dong et al., 2021). Endocrine resistance has been associated with downregulation of ER expression, enabling progression of hormone independent growth in ER+ MCF-7 breast cancer. Shrihastini et al., 2021, have proposed that tumours lose ER expression over time on treatment with aromatase inhibitor. Thus, this study suggested that inhibition of PI3`K/AKT/mTOR as the way by which increasing ER levels could be used to improve hormone dependence, and thereby improve sensitivity towards endocrine treatments (Shrihastini et al., 2021).

Furthermore, activation of PI3`K may be associated with estrogen resistance in ER+ tumours in patients with overexpression of her2, or fibroblast growth factor receptor FGFR 1, due to induction of the hormone –independent pathway (Dong et al., 2021& Phung et al., 2022).Thus, clinical studies suggested that using HER2 or ER inhibitors in combination with PI3`K pathway inhibitors might provide more beneficial outcomes in treatment of ER+ breast cancer (Dong et al., 2021 and Phung et al., 2022). Preclinical studies (Akt, Pathways and Su, 2022 and (Dong et al., 2021) reported that inhibition of the PI3`K pathway may be involved in increasing the activity of Raf/ MEK/ ERK pathway due to loss of feedback inhibition. mTORC1 is one of the convergence points between the two pathways. It has been found that blocking PI3`K activity leads to an increase in MAPK/ERK pathway activation, this activation occurring through an S6K-PI3`K feedback loop. Therefore, these studies have suggested that dual inhibition of both PI3`K and MEK/ERK pathways could lead to more effective growth inhibition rather than a single pathway inhibition.

3. Effect of estrogen in induction of apoptosis

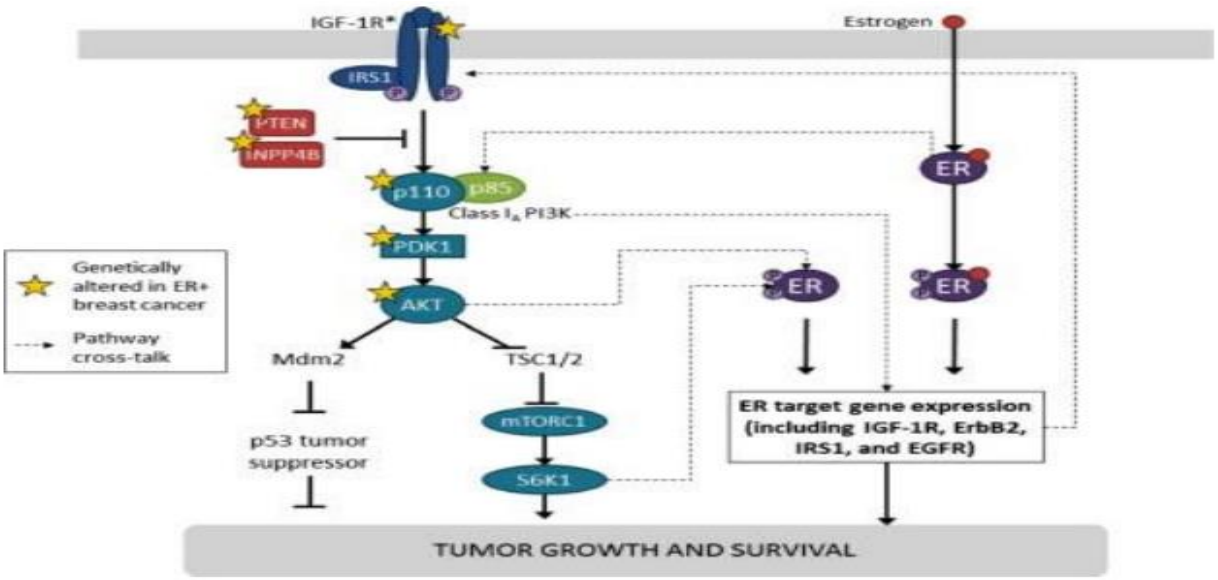
Apoptosis is a programmed cell death, which functions to maintain tissue homeostasis. It plays a crucial role in removing dead cells. There are two main ways to induce apoptosis, namely the extrinsic and intrinsic pathways. The intrinsic mechanism is mediated by the Bcl-2 protein family which includes proapoptotic and antiapoptotic members. Pro apoptotic family members include Bax, Bak, & Bok which are activated upon oncogene activation or DNA damage. Meanwhile anti-apoptotic members like Bcl-2/Bcl-xL can cause cancers by blocking cell death and enabling cell survival. Overexpression of anti-apoptotic factors, results in inhibition of the proapoptotic action. The Bcl-2 family functions to regulate apoptosis via induction of cytochrome c release through disturbing mitochondrial membrane

permeability (Chimento et al., 2022). The second pathway, (extrinsic), includes the receptors of tumor necrosis factor (TNF), TNF receptor 2, CD95/Fas/Apo1, and death receptors 3-6 (DR3-6) (Chimento et al., 2022). This pathway is executed via releasing proteases called caspases upon binding the cell receptor Fas to its ligand. Then activated Fas is capable ofrecruiting adapter proteins, associated with formation of a procaspase-8 complex, which triggers the apoptosis once it is activated (Chimento et al., 2022). The mechanism by which cells trigger the intrinsic apoptosis pathway starts with releasing mitochondrial cytochrome c mediated by Bax, a member of the proapoptotic Bcl-2 family, and loss of mitochondria potential with formation of a complex between Bax and p53, a tumor suppressor protein. The release of cytochrome c, results in activated caspase 9, which then act in proteolytic activation of caspase 3 that initiates the process of cell death.

Dysregulation of the balance between pro-apoptotic and anti-apoptotic members of the Bcl-2 family, would result in apoptosis inhibition and tumorigenesis (Chimento et al., 2022). Also, it is worth noting that poor responses towards hormonal therapy, radiotherapy, and chemotherapy and treatment resistance are likely caused by dysregulation of apoptosis (Chimento et al., 2022). Importantly, E2 has been shown to prevent apoptosis, first through its action in activation of anti-apoptotic proteins like Bcl-xl and Bcl-2 in breast cells like MCF-7, T47D and ZR-75-1 (Chimento et al., 2022).

Second, by E2 action in activation of the AKT pathway, which is associated with phophorylation of Murine Double Minute 2, Mdm2 that results in inhibition of the p53 tumor suppressor protein, that controls the Bax activation, which is important in changing the mitochondrial membrane integrity, causing cytochrome c release (Shrihastini et al., 2021), as seen in figure 2. In addition, activated AKT may lead to activation of anti apopototic genes such as Iκ B, inhibitor of NF-κB, and kinase IKK, a primary regulator of NF-κB activity (Chimento et al., 2022).

Figure (2): Based on Ciruelos Gil, 2014, showing the interaction between ER and the PI3`K/AKT/mTOR pathway in breast cancer.



4. Role of estrogen metabolism in induction of breast cancer

In addition to E2 dependent ER, E2 can also promote breast cancer due to its metabolites independently of ER. Estrogen metabolism includes several very important pathways that can possibly induce de novo DNAmutation. These pathways include:2, &4-hydroxylation, 16 α hydroxylation and 4 hydroxyestradiol-quinone-adenine/guanine adduct depurination, which subsequently participate in DNA damage that can lead to breast cancer. The estrogen and estrone are metabolized to produce 3,4 and 1,2 catechols and 16- α OH estone. These then undergo further metabolism to produce 3,4 & 2,3-quinones, that are associated with production of reactive oxygen species (ROS), aided by cyctchrome p450 reductase as shown in figure 3, which results in DNA damage (Yue et al., 2013). In addition, the metabolism of 3,4 quinone can involve inducing DNA mutations, which can be considered a risk factor for developing breast cancer as explained in figure 4.

Figure (3): Based on Yue et al., 2013, showing estrogen synthesis and metabolism.

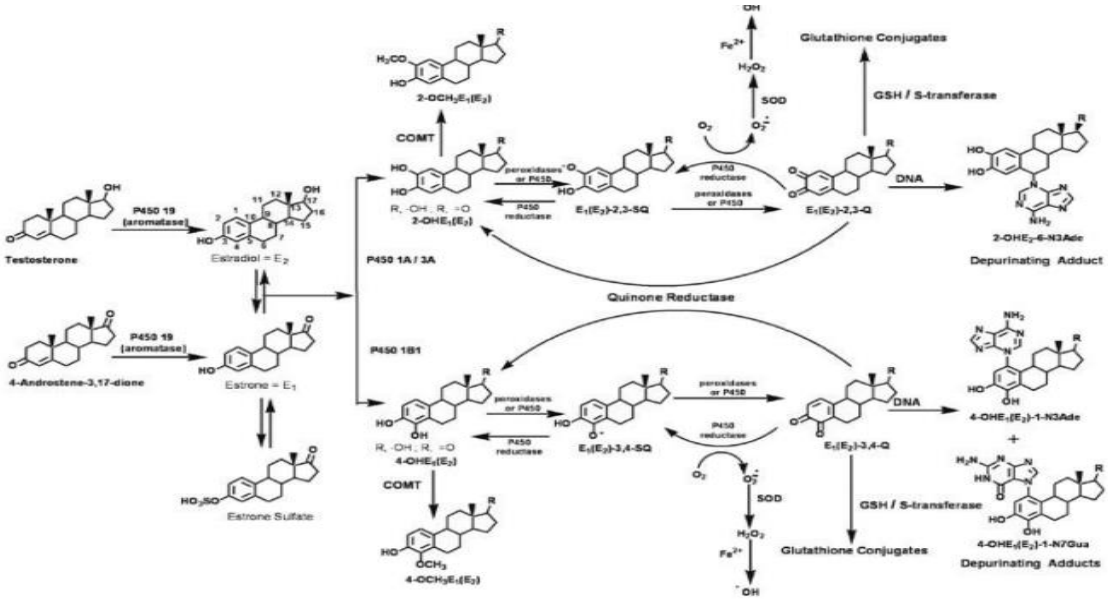
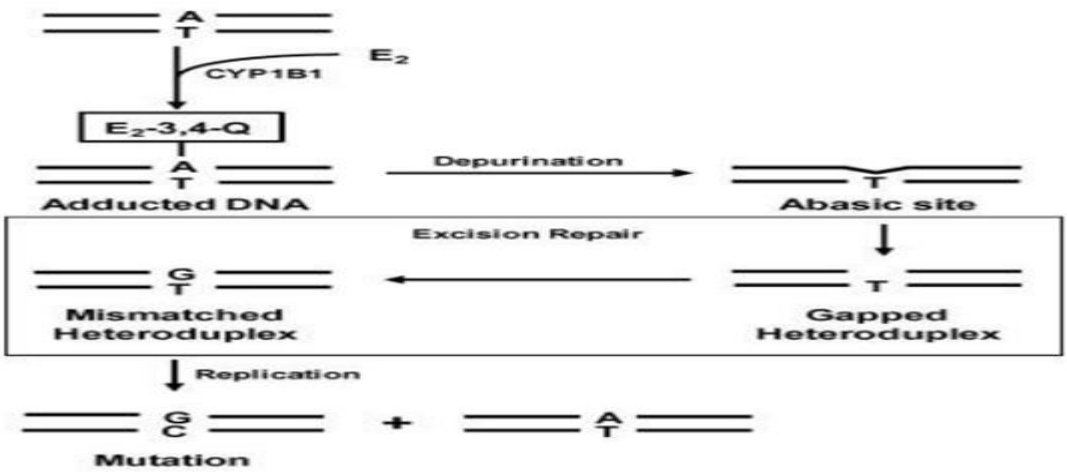


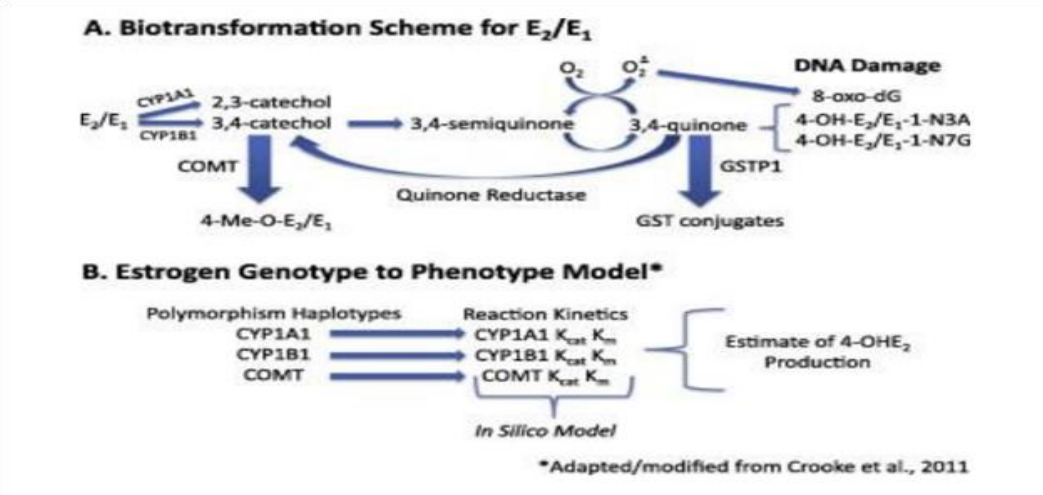
Figure 4: Based on Yue et al., 2013, explaining DNA mutations that resulting from depurinating adduct.



The study by (Yue et al., 2013) which found a strong link between estrogen metabolism and induction of breast cancer raises the question of why women have different susceptibilities to breast cancer. Indeed, it was found that polymorphisms in estrogen metabolism genes which unbalance estrogen metabolism is the main reason for inducing unstable adducts of DNA that participate in breast cancer. For instance, the presence of essential enzymes such as quinine reductase QR, glutathione transferase GSTand catechol-O-methytransferase COMT will act to prevent quinine, semiquinone and catechol formation. In addition, recent research referred to COMT's importance in methylation of catechols at the positions of 2,3, and 4 that might play a role in both preventing estrogen binding to its receptor and in converting them to the active quinone form that might prevent formation of depurinating adducts, and DNA oxidative damage.

Thus, either estrogen metabolism unbalance or enzyme polymorphisms may be associated with women with different predisposing factors towards breast cancer; details are explained in figure 5.

Figure (5): Based on (Yue et al., 2013. Scheme A, showing both E2 estrogen and estrone E1 biotransformatioms, while B representing phenol and genotypes of estrogens.



5. Approaches to developing breast cancer therapy

The majority of breast cancer treatment involves a hormone based therapy, for example blocking of the estrogen receptor on cancerous cells by inhibition of binding of ER to estrogen, using drugs such as tamoxifen, or preventing estrogen synthesis with an aromatase inhibitor, or reducing ERα levels using a pure antiestrogen such as fluvestrant.

Tamoxifen, was a common and reliable kind of drug to treat breast cancer, but unfortunately, tamoxifen interactions with many growth factors was one of the reasons which lead to tamoxifen resistance. Also, tamoxifen can inhibit the estrogen dependent pathway only. These reasons together make tamoxifen only a partially effective agent in breast cancer, and alternative approaches such as aromatase inhibitors, e.g. exemestane are being actively developed for breast cancer treatment. Aromatase inhibitors block both estrogen-dependent and independent pathways, and may lead to decreased motility rate (Costa & Vale, 2022).

Tumors' resistance to chemotherapy represents a major challenge of breast cancer disease. As explained earlier, some tumors became resistant and had no response during the treatment period. There are many factors associated with resistance to chemotherapy. From these factors, it is

believed that disturbance of the balance between cell proliferation and apoptosis may be a factor for resistance, which is observed in cancerous cells positive for estrogen receptor (ER+) (Chimento et al., 2022).

Estrogen`s effect involves inducing apoptosis in several ways. First, E2 can induce apoptosis through activation of the extrinsic apoptosis pathway that involves activation of Fas/FasL death signaling. This is achieved through estrogen receptor promoting the interaction of transactivating factors including specificity protein1(SP-1) and activator protein (AP-1) with DNA bound factors in the promoter region at GC boxes, resulting in upregulating FasL binding receptor which initiates the apoptotic signaling pathway.

Second, E2 was recently found to induce the apoptosis through activating the intrinsic pathway. MCF-7- E2 treated cells increase the expression of 34 pro-apoptotic proteins such as Noxa, p53, Bax, and Bim and also release cytochrome c from mitochondria, resulting in activation of caspases 7& 9 with cleavage of poly ADP-ribose polymerase. Further, E2 can block AKT phosphorylation of NF-κB, a nuclear factor-kappa-B which is involved in the cell survival pathway, to induce the apoptotic pathway. For example, through E2 treatment for tamoxifen resistant MCF-7 tumor cells, a downregulation of NF-κB, will result in reduction of cyclooxygenase 2 COX-2, an NF- κB- responsive gene (Fan & Jordan, 2022). Taken together the findings above imply that if apoptosis could be promoted by inhibition of survival pathways, responses to breast cancer treatment would improve.

6. Breast cancer and endocrine resistance

Endocrine resistance is considered one of the most permanent problems that can reduce the benefits of breast cancer treatment. Numerous mechanisms can result in poor treatment responses of breast cancer patients. These include: alteration of microRNAs expression, polymorphisms occurring in tamoxifen metabolism, and using reductant alternative signaling pathways. MicroRNAs (miRs) are a non-coding RNA which can modulate the expression of particular proteins through suppression of protein synthesis or degradation of mRNA. Alteration of MicroRNAs gene expression is believed to be one of the reasons for breast cells tamoxifen resistance and a recent study found some alterations of miR gene expression in MCF-7. Over expression of different miR profiles, miR-221 and miR-222 in ER+ increased the resistance towards tamoxifen, whereas knockdown of miR 221 and miR-222 genes was associated with induction of apoptosis and cell growth arrest (Chien, 2021). Second, it is believed that the interaction between growth factors and ER may be a reason for endocrine resistance. Growth factor proteins include, IGF1R, EGFR, and HER2 could activate the PI3`K and MAPK pathways which affect proliferation and survival of cells, and might result in endocrine resistant breast cells (Lasagna et al., 2022). For example, both EGF and IGF play a crucial role to increase breast cancer cell proliferation by about 60-70% compared to control (Tsonis et al., 2013). The synergistic effect between E2 and growth factors is explained through decreasing E2 proliferative responses when the IGF-IR or EGFR of mice are knocked out (Fuentes & Silveyra, 2019). Recent studies have reported that E2 can induce crosstalk between ERs, and membrane associated growth factors :IGFR and EGFR, resulting in breast cancer progression. In other words, when ER is activated due to increased phosphorylation of ER in response to growth factor signaling, this activates transcription of estrogen-regulated genes even in the presence of anitestrogen agents, leading breast cells, MCF-7 (overexpressing ER and HER2) to be resistant to tamoxifen. EGFR induces tamoxifen resistance via activation of ER AF-1 and increases tamoxifen agonistic behavior (Chien, 2021). Thus, using selective growth factors inhibitors may be one effective therapeutic method in breast cancer treatment. In addition, endocrine resistance may be

caused by genetic coregulators which include coactivators and corepressors. High levels of coactivators, such as SRC-3, or a reduction in corepressor activity can convert tamoxifen from antagonist into agonist, resulting in tamoxifen resistance (Beilner, 2022; Chien, 2021). Metabolism of tamoxifen may be another factor might be associated with tamoxifen resistance. Tamoxifen is metabolized in the liver to N desmethyltamoxifen and 4-hydroxytamoxifen in the presence of cytochromes p450: CYP3A4 and CYP2D6, that can be further metabolized into endoxifen. Production of 4-hydroxytamoxifen and endoxifen could impact cell proliferation through an exhibition of high affinity towards ERs resulting in cell proliferation suppression. Expression of p450 species could be impaired by tumors leads to tamoxifen resistance. In this case, gene therapy can effectively improve tamoxifen responses through increasing p450 activity via flavoenzyme NADPH-450 reductase (Opitz, Ostroff and Whitman, 2020; Bezerra et al., 2018)

It is worth mention that administration of other drugs to the patients who are already treated with tamoxifen can induce drug resistance. As an example, administration of antidepressant drugs have been found to inhibit cytochrome CYP2D6, resulting in blocking endoxifen production and limiting the efficiency of breast cancer treatment (Chan et al., 2020). Taking all previously hypothesized mechanisms that can associate with induction of endocrine resistance, most proposed therapeutic strategies will be based on a combination of drugs targeting various pathways alongside endocrine therapy that may improve the outcomes of endocrine responses in resistant breast cancer cells.

7. CONCLUSION

Estrogen binding to its receptors leads to regulation of gene expression either by direct binding to the ERE to then transactivate target transcription or by estrogen receptor interaction with other transcriptional factors such as AP-1 or SP-1. This review looks at current facts connecting the in cooperation between ER-dependent and -independent mechanisms. It has been shown that both mechanisms are associated with carcinogenic process and with development of breast cancer. Estrogen metabolites can be also involved in progression of breast. Thus, the current review support the roles of ER dependent and independent actions in the carcinogenic process and using anti-estrogens block only receptor mediated pathways while, the aromatase inhibitors block both pathways.

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