TITLE:

Nuclear and Extranuclear-Initiated Estrogen Receptor Signaling Crosstalk and Endocrine Resistance in Breast Cancer

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ABSTRACT

Estrogens regulate function of reproductive and non-reproductive tissues in healthy and diseased states including breast cancer. They mainly work through estrogen receptor alpha (ER α) and/or estrogen receptor beta (ER β). There are various ER α targeting agents that have been used for treatment of ER (+) breast tumors. The impact of direct nuclear activity of ER is very well characterized in ER (+) breast cancers and development and progression of endocrine resistance. Recent studies also suggested important roles for extranuclear-initiated ER α pathways, which would decrease the potency and efficiency of ER α targeting agents. In this mini-review, we will discuss the role of nuclear and extra-nuclear ER signaling and how they relate to therapy resistance in breast cancer.

INTRODUCTION

Estrogen receptor alpha (ER α) and estrogen receptor beta (ER β) are members of the Type I nuclear receptor superfamily. They regulate 17 β -estradiol (E2)-mediated transcriptional activation of responsive genes. In the last three decades, various agonists and antagonists have been designed for the treatment of ER-positive breast cancer. Although long-term usage causes resistance, tamoxifen is still the most popular endocrine agent for ER (+) breast cancer treatment. This mini-review aims to highlight recent studies that uncovered the importance of ER α and kinase signaling pathway crosstalk in therapy resistance for breast cancer.

1.1. Estrogen Receptors (ERs)

1.1.1. *ER function in physiology*

Estrogen receptors belong to the Type I Nuclear Receptor Super Family that comprises classical steroid receptors. There are two different forms of estrogen receptors, known as estrogen receptor alpha (ER α) and estrogen receptor beta (ER β). Both receptors can act as transcription factors or initiate extranuclear-initiated kinase signaling cascades. ER α is the first steroid receptor to be discovered by Jensen in 1958. After almost 20 years another ER was discovered [1, 2]. They are encoded by genes that are on different chromosomes, have tissue specific expression profiles, and have distinct functions. While ER α is mainly expressed in breast, uterus, prostate, brain, liver, adipose tissue and bones, ER β is widely expressed in the ovary, prostate, testes, lung, thymus, spleen, bone marrow, salivary gland and vascular epithelium. ER α and ER β usually act in opposite ways. In breast tumors, ER α expression is high, but presence of ER β correlates

with better prognosis by modulating the effects of ER α [3]. Estrogens play critical roles for maintenance and development of reproductive and non-reproductive tissues since lack or excess of estrogens cause various pathological conditions human breast, ovarian, colorectal, prostate and endometrial cancers, osteoporosis, atherosclerosis, metabolic syndrome and Alzheimer's disease [4, 5]. ER α is a major player in breast cancer, and its expression correlates with better prognosis [6].

1.1.2. ER structure

ER α (NR3A1) and ER β (NR3A2) are encoded by two different genes called *Esr1* (on 6q21.5) and *Esr2* (on 14q.21), respectively. ER α and ER β isoforms show tissue-specific expression and they also have been shown to form heterodimers on binding estrogen receptor elements (EREs). Although there is a high homology between DBDs (~95%) and LBDs (~50%) of ER α and ER β , N-terminal domains show only 15% sequence similarity [7]. ESR1 gene consists of 8 exons and it is located on chromosome 6q25.1. It is expressed under control of 6 tissue-specific promoters. The full-length size protein product is 66 kDa [8]. Starting from N-termini, ER α has 6 domains which are named from A to F. A/B domains are the N-terminal domain and have 180 amino acids functioning as AF-1. This region possesses a molecular recognition region (ID region), mostly carrying a random coil structure [9]. The N-termini domain can activate transcription even in the absence of the hormone by means of phosphorylation of the receptor at serine-118 and serine-167 residues by MAPK and Akt pathways, respectively. AF-1 domain can also modulate the response to SERMs together with the domain F called AF-2. Both A/B and E domains are required for full agonist action [10, 11]. C domain is referred DNA binding domain (DBD) and located between amino acid 181 and 263. It has an evolutionary conserved helix-loop-helix structure, which has two cysteine rich zinc finger motifs that interact with a palindromic (GGTCAnnnTGACC) sequence on DNA. The ER DBDs have two sub-domains which are different in term of structure and function. Proximal box, P-box, is the first sub-domain which is responsible for the interaction with the sugar-phosphate backbone on the major DNA groove of the ERE. D-box is the second sub-domain and it is important for receptor dimerization [7, 12]. Between amino acids 264 and 302, resides the D domain and carries a nuclear localization signal. This hinge region serves as a flexible connection between DBD and LBD. E/F domains between amino acid 303 and 533 are LBD and they consist of 12 helices which is critical for hormone binding and dimerization. On the far C-termini of ER, there is F domain serves as

AF-2. This region works synergistically to maximize transactivation function together with AF-1 [7]. Recently, several mutations in F-domain were identified in more than 30% of the metastatic ER α (+) tumors. These mutations render the receptor constitutively active and decreases inhibition of the receptor action by currently available endocrine therapies [13-17].

1.1.3. ER ligands

17 β -estradiol (E2) is synthesized from cholesterol and it is the endogenous ligand of ERs. Estrogen was purified and crystalized by Edward Doisy and Alfred Butenandt nearly simultaneously in 1929 and later 17 β -estradiol (E2) biosynthesis was shown to be achieved by aromatase enzymes mostly in the ovaries, adipose and adrenal tissue [18]. With the discovery of the chemical structure of estrogen by using new molecular biology techniques, a variety of physiologic effects on different tissue types were also identified. These studies showed that estrogen was a good candidate to manage menopausal symptoms of women during 1970s. In these studies, it was shown that 17 β -estradiol (E2) is a steroid hormone, whose synthesis is regulated by 17-hydroxysteroid dehydrogenase. The human aromatase is encoded by *CYP19A1* gene and the size of the full protein is about 123 kDa. First exon is expressed in tissue-specific manner [19]. Tissue-specific expression of aromatase regulates 17 β -estradiol (E2) synthesis in the body.

The LBD domain of ERs bind to both agonists and antagonists, but helix 12 has distinct orientations with different ligands. Upon agonist binding, including the 17 β -estradiol (E2) and the synthetic nonsteroidal estrogen diethylstilbestrol (DES) to ERs, helix 12 on LBD folds against helices 3 and 11 which allows maximal coactivator binding on TAD. However, this coactivator binding pocket is disrupted with antagonist binding such as selective estrogen receptor modulators (SERMs). In this region, long hydrophobic groove on helix 12 becomes available for corepressor binding [20, 21]. Tamoxifen and raloxifene are two SERMs and they can act either as an agonist or as an antagonist in different tissues [22]. Raloxifene acts as an ER antagonist in the breast and uterus, yet it has agonistic effects on bone structure, which provides increase in mineral density to improve menopausal osteoporotic outcomes. Tamoxifen is the most commonly used endocrine agent which is still prescribed to treat premenopausal and postmenopausal breast cancer patients. Tamoxifen has tissue specific activity; it is antagonistic in breast tissue, yet it acts as an agonist in the uterus. While it blocks AF-2, it can activate AF-1 in tissue specific manner [23]. In addition, with long-term usage, cancer cells might develop tamoxifen resistance. The

molecular mechanism behind tamoxifen resistance is an active area of research by many labs and several mechanisms will be discussed in Section 3.3.

1.1.4. Post-translational modifications (PTMs) and interacting partners of ER

ER activity can be modulated by posttranslational modifications and/or differential interactions with coactivator or corepressors. [24-27]. ER α is phosphorylated at different serine residues on N-terminal transactivation domain, DBD and a Tyr residue in the LBD [28-33]. Kinases downstream of mitogen-activated protein kinase (MAPK) pathway and protein kinase pathway (PKA) increases phosphorylation of ERs [31, 34-36]. The DBD of ER is also acetylated by p300 coactivator associated factor (PCAF) on four highly-conserved lysine residues which control the transcriptional activity of ER [37]. In addition, palmitoylation of human ER α protein on Cys-447 enables membrane association of the receptor. Studies using mice that has mutation on this residue showed that membrane-specific loss of function resulted in female infertility with abnormal ovarian function and abrogated significant vascular actions of E2 [38]. Moreover, palmitoylation affects dimerization, protein-protein interaction partners and E2-dependent degradation of the receptor as well as the phosphorylation of the ER α Ser-118 residue [39, 40]. Sumoylation is another important PTM and it usually promotes autophagy and apoptosis under stress conditions. In parallel to this function, sumoylation of ERs leads to transactivation of some cell death-related genes in presence of endogenous ligands [41]. Regulation of ER degradation is also controlled by ubiquitination. In recent articles, it has been shown that, E2-mediated ER α degradation requires ubiquitination of residues such as leucine 429 and alanine 430 on LBD [42]. A comprehensive evaluation of PTMs of ER α in breast cancer revealed several sites associated with better clinical outcome for tamoxifen therapy, whereas other phosphorylation sites were associated with poorer clinical outcome. ER α acetylation and sumoylation have also been shown to be important predictors of breast cancer outcomes [43].

Numerous ER α interacting partners have been identified in the last two decades. Steroid receptor co-activator (SRC-1) was the first nuclear receptor co-activator to be identified; it stimulates transcriptional activation by binding to AF-2 region of nuclear receptors including ER in presence of the ligand [44]. In the late 1990s, SRC-3 and receptor interacting protein 140 (RIP140) were identified as two important key co-regulators of both ER α and ER β [45, 46]. ERs also interact with other transcription factors, nuclear receptors and coregulators associated with these proteins. Vitamin D receptor interacting protein (DRIP)/ thyroid hormone receptor associ-

ated proteins (TRAP) complex, nuclear receptor corepressor (NCoR) and silencing mediator for retinoid and thyroid receptor (SMRT) interact with ER α through AF-2 domain [47-49]. Recent studies also showed that ER α physically interacts with c-MYC through AF-1 to stabilize estrogen-mediated signaling networks [50]. The retinoic acid receptor alpha (RAR α) was also shown to be in ER complex and is important for maintenance of ER-cofactor interactions. These data suggests that ER α interacts with different nuclear receptors to provide effective transcriptional activity in breast cancer cells [51].

1.2. ER activated pathways

1.2.1. *Nuclear initiated pathways*

In the absence of ligand, ER α binds to heat-shock proteins in the cytoplasm. In presence of the hormone, ER disassociates from HSPs, translocates into the nucleus and binds to EREs on the genome. Once ER α binds to EREs, it recruits other co-regulators to form a transcriptional regulatory complex. Then, the complex recruits basal transcription machinery and RNA Polymerase II to the proximal promoter region. Some of the genes lack any ERE-like sequences and they require another transcription factor to provide the scaffold for ER to indirectly bind to DNA. Most of the primary E2-responsive genes are activated through the direct/indirect interaction between ER and DNA. On the other hand, secondary E2-responsive genes are the ones whose expression depends on a transcription factor, which is activated by ERs [52, 53]. Many studies identified E2-regulated genes using genome-wide cDNA microarray and high-throughput RNA sequencing technologies [46, 53-62]. The majority of these analyses focused on upregulated genes and several of them characterized different mechanisms by which ER α represses transcription [63-65].

1.2.2. *Extracellular initiated pathways*

Estrogens are also capable of activating extranuclear-initiated kinase signaling, which contributes to gene transcription, cytoskeletal remodeling, cell proliferation and cell survival [57-59, 66, 67]. G-protein coupled ERs (GPER or GPR30) which are located on plasma membrane [68] activate MAPK and PI3K pathways in the presence of estrogens [69]. G protein coupling enables rapid estrogen activated signals to be transmitted by phospholipase C-dependent IP₃ production, which cause an increase in the level of second messengers like calcium and nitric oxide (NO) in several endometrial, granulosa, smooth muscle, duodenum cell lines [70, 71]. Recent studies have shown that GPR30 specifically binds to estrogens and is able to mediate non-genomic es-

trogen actions through epidermal growth factor receptor (EGFR) pathway, the Notch signaling pathway and the mitogen-activated protein kinases (MAPK) pathway [72, 73].

Most recent studies have shown that ERs control cell metabolism and cell proliferation through modulation of other transcription factors and developmental pathways. For example, ER α regulates hypoxia-inducible factor 1 (HIF-1) pathway associated with antiestrogen response in breast cancer [74]. Yu et al. have also found that ER β regulates genes targeted by Hedgehog-signaling pathway [75]. Membrane receptor actions are important in estrogen-mediated regulation of cardiovascular system and nervous system [76, 77]. For example, the membrane-initiated rapid E2 signaling is effective in hypothalamic and hippocampal neurons and this mechanism regulates energy balance, thermoregulation and proliferation in neural tissue by inducing neural protection [78, 79].

Besides secondary messenger signaling, ER α upregulates cell proliferation and cell migration through interactions with IGF-1R and mitogen-activated protein kinase (MAPK) pathway in various cancer cell lines [80-83]. The interactions between ER α localized at the plasma membrane and various specific membrane proteins, such as modulator of non-genomic activity of estrogen receptor (MNAR), Shc, EGF and IGF-1 receptors play important roles in non-genomic estrogen signaling [84-87]. Not only plasma membrane proteins, but also membrane lipids are associated with the small amount of ER α localized on the plasma membrane. Sphingosine-1 phosphate kinase (SphK1) is an enzyme which produces sphingosine-1 phosphate (Sph1) and very recent studies show that increased SphK1 expression is associated with E2-dependent activation of MAPK and intracellular Ca²⁺ mobilization in ER α -positive MCF-7 breast cancer cells [88, 89].

Endogenous ligand 17- β -E2 activates both nuclear and extranuclear-initiated ER pathways. Recent studies using estrogens conjugated to dendrimers that would stay outside the nucleus[60, 90] or modifying the ligand structure so that the ligand cannot form long-lived stable coregulator complexes[59] achieved preferential activation of these pathways. These tools were very useful and enabled researchers to show functions of extranuclear ER-initiated pathways are important in vascular protection, bone physiology and metabolic tissue function [59, 91, 92].

1.3. The Role of Estrogen Receptor in Breast Cancer

1.3.1. *Breast Cancer Incidence and Risk Factors*

According to ASCO, in 2016, almost 240,000 women will be diagnosed with breast cancer and 40,000 deaths due to breast cancer will occur in the United States [93]. Due to delayed childbearing and decreased number of births, the long-term incidence of breast cancer has increased during the last decade. Yet, breast cancer mortality decreased by means of early detection and newly developed treatment strategies [94]. Unmodifiable risk factors can be sourced from both hereditary and hormonal dysfunctions. The most important genetic determinant of breast cancer is *BRCA1* and *BRCA2* tumor-suppressor gene mutations which are inherited in an autosomal dominant manner. *p53*, *PTEN* and *CHEK2* mutations are also other key markers of breast cancer development [95-98]. Another important risk factor is age. Statistics show that the lifetime breast cancer risk for a women increases with advancing age [99, 100]. Besides hereditary factors, hormonal factors also contribute to the risk factors of breast cancer. The effect of high estrogen and progesterone exposure in different stages of lifespan increases the risk of breast cancer [101]. However, almost 80% of breast cancers stem from modifiable factors such as obesity, high-fat intake and excess alcohol consumption [102-104].

1.3.2. Molecular Heterogeneity of Breast Cancer

Breast tumors display varying degrees of molecular heterogeneity since different subtypes are initiated from different cell types in the breast tissue [105-107]. In the clinic four main subtypes are used for classification and treatment decision of tumors: luminal A and B, HER-2 (human epidermal growth factor)/ERBB2 and triple negative/basal like. This classification is based on presence of ERs and HER-2 receptors in the tumor [108]. Almost two thirds of breast cancers are categorized under luminal type [109, 110]. The luminal A/B types are ER (+) whereas, triple negative/basal-like and HER-2 types do not express ER. Luminal A type tumors grow slowly and almost 90% of these tumors can be treated with estrogen receptor mediated targeting strategies. Compared to luminal A type, luminal B tumors are more aggressive; their progesterone receptor (PR) expression is lower and they respond poorly to hormone therapy. Gene expression profiling studies elucidated that luminal B type might display both luminal A type and HER-2 form characteristics. For example *ESR1*, *FOXA1* and *BCL2* gene expression profiles in luminal B type is similar with luminal A type. On the other hand, luminal B type tumors also have similar *MK167*, *BIRC5* and cyclin B1 gene expressions like HER-2 subtype [111]. In clinic, luminal B type tumors are characterized by having ER+/HER2-/Ki67+ profile [112]. HER-2 oncogene is overexpressed in 70% of HER-2 type tumors which leads to activation of downstream signaling

pathways. *HER-2* amplified tumors have low prognosis rate because of their complex signaling features. In triple negative/basal like tumors, there are no hormone receptors (estrogen, progesterone) or *HER-2* receptors, therefore they tend to be more aggressive. There are several subtypes of triple negative breast cancers. One of these subtypes is basal-like tumors. However, not all basal like tumors are triple negative [110]. Since they do not have a potential therapy target, survival rate of the patients who have triple negative tumors is lower than patients who have ER (+) tumors [113].

Mutations in ER (+) tumors are considerably more diverse within luminal A and luminal B tumors than within ER-negative subtypes. Recent studies that identified novel mutations in breast tumors showed that the overall mutation rate was lowest in luminal A tumors. *PIK3CA*, *MAP3K1*, *GATA3*, *TP53*, *CDH1* and *MAP2K4* are the genes are mostly mutated in luminal A subtype. Luminal B tumors also have a diverse array of mutated genes such as *TP53* and *PIK3CA* [107]. These mutations contribute to molecular heterogeneity, and this in turn introduces new challenges as increased heterogeneity is associated with increased therapy resistance.

1.3.3. Tamoxifen and Mechanisms of therapy resistance in breast cancer

The tamoxifen (ICI46,474) was synthesized by Dora Richardson in Arthur L. Walpole's research team in 1962 to develop anti-estrogen compounds as contraceptive pill. Later studies showed that tamoxifen was very effective in treating late stage ER-positive breast cancers [114]. Tamoxifen was the first targeted therapy for breast cancer and it improved the survival rates of many women and man who had early and late stage ER (+) breast tumors. Using gene expression analyses, researchers detected a large body of genes which are affected from endocrine therapy. These genes are related to cell proliferation, metabolism and cell invasion and inflammation and immune response [115].

Although tamoxifen has been used for years as the best treatment option for ER (+) breast cancer, studies showed that long-term tamoxifen usage eventually causes relapse in 40% of the patients. [116]. There are several hypotheses to explain the reason behind therapy resistance against tamoxifen in ER (+) breast cancers, which can be grouped under 4 main groups: alterations of ER expression and functions, metabolism of tamoxifen, alterations in co-regulatory proteins and signaling pathways and miRNAs.

The first proposed mechanism is related to direct interaction between tamoxifen and LBD of *ESR1*. Mutations in LBD domain of ER α is present about 30% of patients with metastatic ER (+) breast cancer [117-122]. Specific ER mutations, such as Tyr537Ser, Tyr537Asn and Asp538Gly cause resistance to antiestrogens by changing the LBD of the ER α [17]. Some of these mutations also affected the activation status of signaling pathways, such as IGF-1 [119]. ER β also seems to be important for tamoxifen resistance. Several studies showed that certain splice variants of ER β expressions are correlated with worse outcomes in advanced breast tumors [123, 124]. Some studies suggested that transcriptional repression due to long-term tamoxifen usage might cause overpopulation of ER-negative tumor cells in tumor environment.

Metabolism of the tamoxifen in the tumor or inability of the body to produce functional metabolites are other mechanisms that were proposed for resistance to tamoxifen. In several studies about tamoxifen resistance reported that lower tamoxifen concentration inside of the tumor relative to plasma concentrations is correlated with worse outcome in breast tumors [124]. On the other hand, some studies suggested that increased concentration of certain tamoxifen metabolites can cause agonistic effects in the cancer cell [125].

The third hypothesis for tamoxifen resistance is related to the alterations in co-regulatory proteins and signaling pathways. MAPK, hedgehog, PI3K/Akt and mTOR pathways have been implicated in tamoxifen resistance. [116, 126]. For instance, some studies reported that high HER-2 levels in tamoxifen resistant tumors is associated with high expression of AIB1 (SRC-3) [127]. Moreover, high AIB1 expression is thought to be associated with a worse disease outcome in tamoxifen-treated patients because of HER-2-related agonistic effect on ER [128]. Other coactivators and corepressors, such as RIP140 [129], NCoR [130] and Nkx3-1 [131] were implicated in tamoxifen resistance since their levels correlated with tamoxifen resistance in tumor samples. In addition, some transcriptional factors (e.g. GATA3 and GREB1) were shown to play a role in regulation of ER-target genes leading to endocrine therapy resistance [132, 133]. Like various types of co-regulatory proteins, major signaling pathways also contribute to generate tamoxifen resistance. Several MAPKs (e.g. like ERK1, ERK2 and ERK3) and ribosomal S6 kinase (RSK) phosphorylate AF-1 domain of ERs and activates estrogen-dependent expression [134, 135]. The activation of growth factor signaling elements contribute to tamoxifen resistance. For instance, the direct interaction between IGF-1 receptor and membrane ERs activates estrogen signaling leading to tamoxifen resistance [80]. Furthermore, the interaction between ER α and HER2 cause

phosphorylation of epidermal growth factor receptor (EGFR) [136]. Besides all these factors, E2-mediated cellular localization changes of critical signaling kinases were also found crucial in generation of tamoxifen resistance [57, 137, 138].

As an important regulators of gene expression, the role of miRNAs in tamoxifen resistance has been studied for a while. Recent studies showed that certain miRNAs are regulated by tamoxifen treatment. In fact, some studies suggested that specific miRNA expression patterns (e.g. miR-375, miR-221/222, miR-200, miR-342, miR-519a, miR-22, miR-301, miR-15a/16) can be used as tamoxifen-resistance markers [139-146]. All of these studies concluded that miRNAs may regulate the sensitivity of breast cancer cells to tamoxifen.

1.3.4. ER (+) breast cancers and possible therapy alternatives

Currently, there are several endocrine therapy approaches to treat ER (+) breast tumors such as steroidal and non-steroidal aromatase inhibitors (AI), SERMs (e.g. raloxifen) and selective estrogen receptor down-regulators (SERDs) (e.g. fulvestrant). First of all, AIs are used to block estrogen production especially in post-menopausal women. Aromatase enzymes catalyze estrogen biosynthesis from androgens in both ovaries and adrenal glands and AIs inhibit these enzymes by competing for the natural substrate binding sites. Clinical studies showed that it is an effective strategy specifically for treating post-menopausal women whose tumors are already resistant to tamoxifen [147]. SERMs are receptor antagonists which occupy estrogen receptors and inhibit endogenous estrogen production. SERMs such as tamoxifen and raloxifen are used to treat pre-menopausal or post-menopausal patients, who have increased side-effects with AIs [148]. SERDs are also routinely used as endocrine therapy agents in clinic. Rather than endogenous estrogen inhibition, they block the effects of estrogen at the levels of the receptor by causing degradation of the receptor itself. Tamoxifen is a partial antagonist of ER α in breast tissue and an agonist in endometrium. Unlike SERMs, SERDs like fulvestrant do not have this partial agonist activity in any other tissue [149, 150].

CONCLUDING REMARKS

Studies investigating the details of ER signaling pathways are fundamental for developing new therapeutic strategies against endocrine resistant breast cancer. Despite several different ER targeting strategies developed in the last three decades, tamoxifen is still one of the best endocrine agents. It is still widely used in premenopausal women and postmenopausal women who experience major side effects with aromatase inhibitors. One-third of these patients will have a

recurrence that will decrease survival of the patient. Many labs are still working to develop strategies to overcome tamoxifen resistance in breast cancer patients. The majority of these research efforts have focused on targeting signaling pathways, such as PI3K and mTOR. However, resistance develops in this setting, too and in this case the arising tumors are even harder to manage. Therefore, novel strategies to delay or overcome tamoxifen resistance are needed.

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Figure 1