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A Fundamental Analysis of Breast Cancer's Estrogen Receptor Signaling Pathways

Ali Abbas Sadiq Alqaisi[1], Hawraa Haider Abbas Jasim[2], Areej Haider Saleh[3], Rafal Ayad Kazem[4], Afnan Abbas Fadhel[5], Saja Ali Kashkul[6]
[1]Diyala University, Iraq
[2,3,4,5,6]Alqasim Qreen University, Iraq

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ABSTRACT

Objective: *This mini-review aims to provide a comprehensive overview of estrogen receptor (ER) signaling pathways in breast cancer, emphasizing their implications for therapeutic resistance and novel treatment strategies.* ***Method:*** *A critical analysis of recent literature was conducted, focusing on molecular mechanisms associated with ER signaling, including alterations in the ESR1 gene, PI3K pathway activation, and dysregulation of cell cycle control.* ***Results:*** *Findings reveal that approximately two-thirds of breast cancers are hormone-dependent and rely on estrogen and progesterone receptor signaling for growth. While antiestrogens remain the cornerstone of hormone therapy, resistance often emerges through diverse molecular pathways. The development of resistance has driven the advancement of targeted therapies such as selective estrogen receptor degraders (SERDs) and combination regimens involving CDK4/6 or PI3K inhibitors.* ***Novelty:*** *This review highlights the evolving understanding of ER signaling in breast cancer and underscores the necessity of targeting specific molecular alterations to overcome resistance. By integrating recent advances in molecular oncology, the study supports the development of more personalized and effective therapeutic strategies for hormone receptor-positive breast cancer.*

INTRODUCTION

Breast cancer was the most often diagnosed cancer among the 19.3 million new instances of cancer that occurred globally in 2020; it was only slightly more common than lung cancer, which accounted for 11.7% and 11.4% of new cases, respectively. While breast cancer is the most lethal disease in women (6.9% of deaths in all genders, but 15.5% of deaths in women), lung cancer still accounts for the majority of deaths across all genders (18% of the 10 million cancer deaths globally). Approximately 1 in 100 breast cancers diagnosed in the US occur in males who share the same features as women, despite the fact that breast cancer primarily affects women [1].

The mammary epithelium, whether ductal or lobular, in healthy tissue is made up of two cell types: basal cells, which can mechanically trigger milk secretion due to their muscular contraction activity, and luminal cells, which create milk [2]. Along with the expression of cytokeratins 8 and 18 and the junctional protein EpCam (epithelial cell adhesion molecule), luminal cells also express hormone receptors including estrogen (ER), progesterone (PR), or prolactin receptors [3]. The expression of cytokeratins 5, 14, and 17, P-cadherin, desmosomal cadherins, and other markers linked to smooth muscle are characteristics of basal cells [3–5].

Estrogen, progesterone, and prolactin are the primary regulators of mammary cell development and differentiation. Growth factors including insulin-like growth factor (IGF), fibroblast growth factor (FGF), amphiregulin (AREG), and a member of the epidermal growth factor (EGF) family are also crucial mediators of estrogen in the development of the mammary glands throughout puberty [3,6,7].

The aberrant growth of the breast's lobular and ductal epithelium, which turns malignant and develops into a tumor, is the cause of breast cancer, a complex and very diverse illness. Moreover, intratumoral heterogeneity enhances the capacity of cancer cells to alter their activity and rewire their gene expression profile in response to cues from the surrounding environment.

These traits have a detrimental effect on prognosis and treatment response, and they aid in the development of malignant tumors. In fact, after the cancer has expanded locally, it may become invasive by spreading to other organs such the brain, liver, lungs, or bones [8]. As a result, there are several breast cancers, each with a unique location, histological type, genetic signature, and, most importantly, a reliance on hormones for growth. These variables work together to produce breast tumors with very varied aggressiveness and prognoses, necessitating distinct therapy approaches [9]. An overview of estrogen signaling in breast cancer is intended to be provided by this mini-review, with a focus on the ER alpha subtype's genomic and non-genomic activity.

Additionally highlighted are the primary processes behind hormone treatment resistance in ER-positive breast cancer.

RESEARCH METHOD

2. Background on Breast Cancer

2.1. Classification

Breast cancers are classified in accordance with WHO (World Health Organization) guidelines, which are updated often to enhance patient care [10]. In order to grade the cancer and select the best course of treatment to conquer the illness, tumor classification is essential. For instance, the necessity of hormone therapy or targeted medicines depends on a number of factors, including the existence or lack of hormone receptors.

According to Perou et al. (2000), one of the primary criteria used to categorize breast tumors is their molecular profile [11].

This study used the differential expression of a panel of important genes to show the molecular heterogeneity of breast tumors. Human epidermal growth factor receptor 2 (HER2)-positive (20% of cases), luminal A (50–60% of cases), luminal B (10%), and basal-like triple-negative tumors (approximately 10% of cases) are the four primary groups of breast cancer that can be distinguished from the expression profiles that were obtained. Another subgroup that is similar to the luminal A group but has a worse prognosis has also been characterized as normal-like. Ten percent of the luminal A group is made up of

this subgroup. In routine clinical practice, immunohistochemical markers including ER, PR, and HER2 are typically used to identify these tumor types. Yes,

For prognostic and therapeutic reasons, these tumor-identification indicators can take the role of transcriptome data to match the various forms of breast cancer (Table 1). The least aggressive tumors are luminal ones, which are identified by ER expression. Only type B expresses HER2, and they may also express PR. Because genes like Aurora kinase A and KI-67, which are involved in cell proliferation and the cell cycle, are more highly expressed in luminal B cancers than in luminal A (low proliferative) cancers, the latter are more aggressive. Additionally, luminal-related genes like PR and FOXA1 are expressed less frequently in luminal B cancers [12–14].

like FOXA1 and PR [12–14]. Luminal B cancers are linked to a greater frequency of p53 mutations than luminal A tumors (29% vs. 12%). ER and PR receptors are not expressed in HER2-positive tumors. Increased cell survival and proliferation are the results of overexpressing the HER2 receptor, which also stimulates other signaling pathways including PI3K/AKT (phosphoinositide 3-kinases/protein kinase B) and Ras/MAPK (mitogen-activated protein kinases). This makes this kind of breast cancer more aggressive than luminal tumors and encourages the growth of metastases [9].

Therefore, in comparison to the other groups, basal-like tumors that do not express the three main biomarkers (ER, PR, and HER2) were classified as triple negative. This subtype of breast cancer is characterized by elevated expression of genes linked to proliferation, such as amplification of MYC, CDK6, and CCNE1, as well as keratin 5, keratin 17, intergrin-B4, and laminin. Furthermore, TP53 mutations and altered DNA repair, including loss of BRCA2, PTEN, and MDM2, are characteristics of triple-negative breast cancer. These tumors have a poor prognosis because they are more aggressive and diverse, have a high proliferation index, a high histological grade, and a high risk of both local and distant recurrence [15,16].

Table 1 presents a comparative overview of the four primary molecular subtypes of breast cancer—Luminal A, Luminal B, HER2 Positive, and Triple Negative. The subtypes are differentiated based on hormone receptor status (PR and ER expression), HER2 expression, proliferation rate (Ki67), and associated clinical outcomes. Luminal A and B subtypes exhibit varying levels of hormone receptor expression and are generally treated with endocrine therapy. HER2 Positive tumors are characterized by HER2 overexpression and typically require anti-HER2 targeted therapies. Triple Negative breast cancers lack expression of ER, PR, and HER2, making them more aggressive and responsive primarily to chemotherapy. The table also indicates the proportion of cases, prognosis, and typical therapeutic approaches for each subtype, aiding in clinical decision-making and personalized treatment planning.

Table 1. Molecular Subtypes of Breast Cancer – Characteristics, Prognosis, and Therapies

	Luminal A	**Luminal B**	**HER2 Positive**	**Triple Negative**
Proportion of cases	50%	30%	10%	20%
PR expression	+	++	+	-
ER expression	++	+	-	+
HER2 expression	-	+/-	+	-
Proliferation (Ki67)	high	Low	High	High
Prognosis	Good	Intermediate	Intermediate	Poor
Therapy	Endocrine therapy	Endocrine therapy	Anti-HER2 therapy	Chemotherapy

2.2. Occurrence and Risk Factors

The biochemical pathways leading to the emergence of breast cancer are complex and can be triggered by a variety of risk factors, outlined in Figure 1. These are related to heredity, hormone exposure, lifestyle, food and alcohol intake, obesity and environment [12,17–21]. Less than 10% of breast cancers are caused by genetic or inherited causes. The majority of patients in this situation have mutations in the breast cancer-associated genes BRCA1 and BRCA2, which are involved in DNA repair and cell cycle checkpoint activation.

When these genes are altered, checkpoint control is compromised and chromosomal instability occurs, both of which encourage the growth of tumors [22].

Hormonal exposure is one of the biggest hazards for breast cancer. Breast cancer risk is raised by prolonged exposure to endogenous and exogenous estrogen [23]. It's also important to remember that hormonal menopausal therapy, which consists of estrogen and progestin, has been linked to a higher risk of invasive and in situ breast cancers [24].

Studies on androgens are conflicting and fail to clearly link the risk of breast cancer to circulating androgen levels [25]. Nonetheless, McNamara et al. demonstrated that elevated levels of testosterone in the blood seem to raise the risk in premenopausal women [26].

A high blood testosterone level in postmenopausal women may also be a significant predictor of breast cancer recurrence [27]. Breast carcinogenesis is also thought to be influenced by environmental factors like ionizing radiation, air pollution, heavy metals, and long-term exposure to chemicals like polychlorinated biphenyl, polycyclic aromatic hydrocarbons, organic solvents, and organochlorine insecticides and pesticides [28–30]. The risk factors are more prominent in industrialized nations, where lifestyles are more sedentary, breastfeeding is less common, first pregnancies occur later, and hormone therapies are more commonly utilized.

This indicates why the incidence rate of breast cancer is more than in developing countries, although the fact that screening campaigns are less extensive. However, changing lifestyle in developing nations and Asia are contributing to a rise in breast cancer occurrence and, subsequently, in breast cancer death. The implementation of preventive and early detection initiatives is therefore particularly vital to counter the growth of this malignancy, especially in poor countries [1].

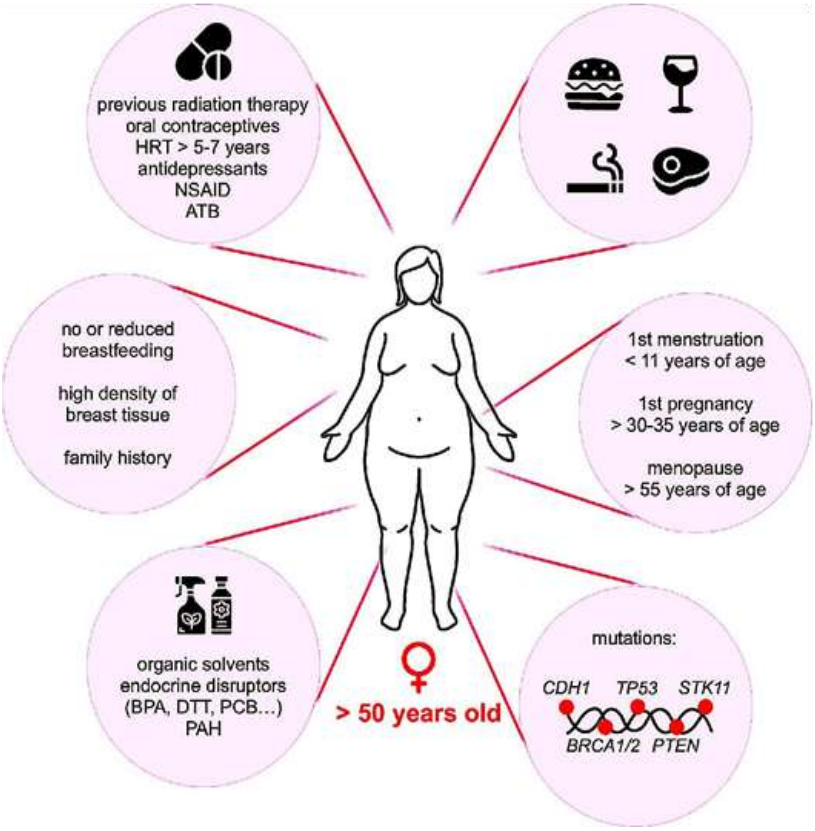

Figure 1. Major Risk Factors Associated with Breast Cancer in Women Over 50 Years of Age

Figure 1 breast cancer risk factors. Both environmental and genetic factors contribute to breast genetic as well as environmental factors participate in breast cancer development. ATB: antibiotics DTT: dichlorodiphenyltrichloroethane; BPA: bisphenol A;

cancer cell survival [31], such as the overexpression of oncogenes like MYC, a transcription factor that promotes the production of genes essential for cell survival and proliferation. Through both gene transcription and protein stability, MYC expression is elevated in several different human malignancies outside breast cancer [32, 33]. Likewise, it is common to see overexpression or activation of receptor tyrosine kinases and associated signaling pathways, such as the HER2 family or EGFR1 (Epidermal Growth Factor Receptor 1). These factors' activation triggers a variety of signaling pathways that control cell survival and proliferation, including Ras/MAPK, PI3K/AKT, and PLC/PKC (Figure 2). Within this family, breast cancer growth is influenced by the overexpression of EGFR1 and HER2 [34]. The receptor for the IGF1 protein, known as Growth Factor 1 Receptor, is crucial for the growth and operation of the mammary gland. When IGF1 binds to its receptor, IGF1R is phosphorylated, activating the PI3K/AKT and Ras/MAPK signaling pathways with proliferative and anti-apoptotic properties (Figure 2).

Increased circulating IGF1 levels or overexpression of IGF1R can overactivate these pathways, which aids in the unchecked growth and survival of breast cancer cells [35]. Lastly, the carcinogenesis of breast tissue may be facilitated by the loss of expression or function of tumor suppressor genes like BRCA1 and BRCA2. These genes produce proteins that aid in homologous recombination, which repairs DNA double-strand breaks. These DNA repair pathways are changed when these genes are mutated.

This raises the possibility of developing mutations and aids in the emergence of certain malignancies, including ovarian and breast cancers [36]. e development of many cancers, especially those of the breast and ovary [36]. It is also important to note that the TP53 gene encodes the p53 protein, a transcription factor that, in response to a variety of cellular stresses (DNA damage, hypoxia, oxidative stress, etc.), activates the expression of genes involved in cell cycle arrest or apoptosis. This antiproliferative activity is then necessary to prevent the development of cancer cells, which explains why TP53 mutation plays a significant role in many cancers, including breast cancer [37]. Additionally, the PTEN (Phosphatase and Tensin homolog) gene encodes a phosphatase that contributes to the inhibition of the PI3K/AKT pathway (Figure2).

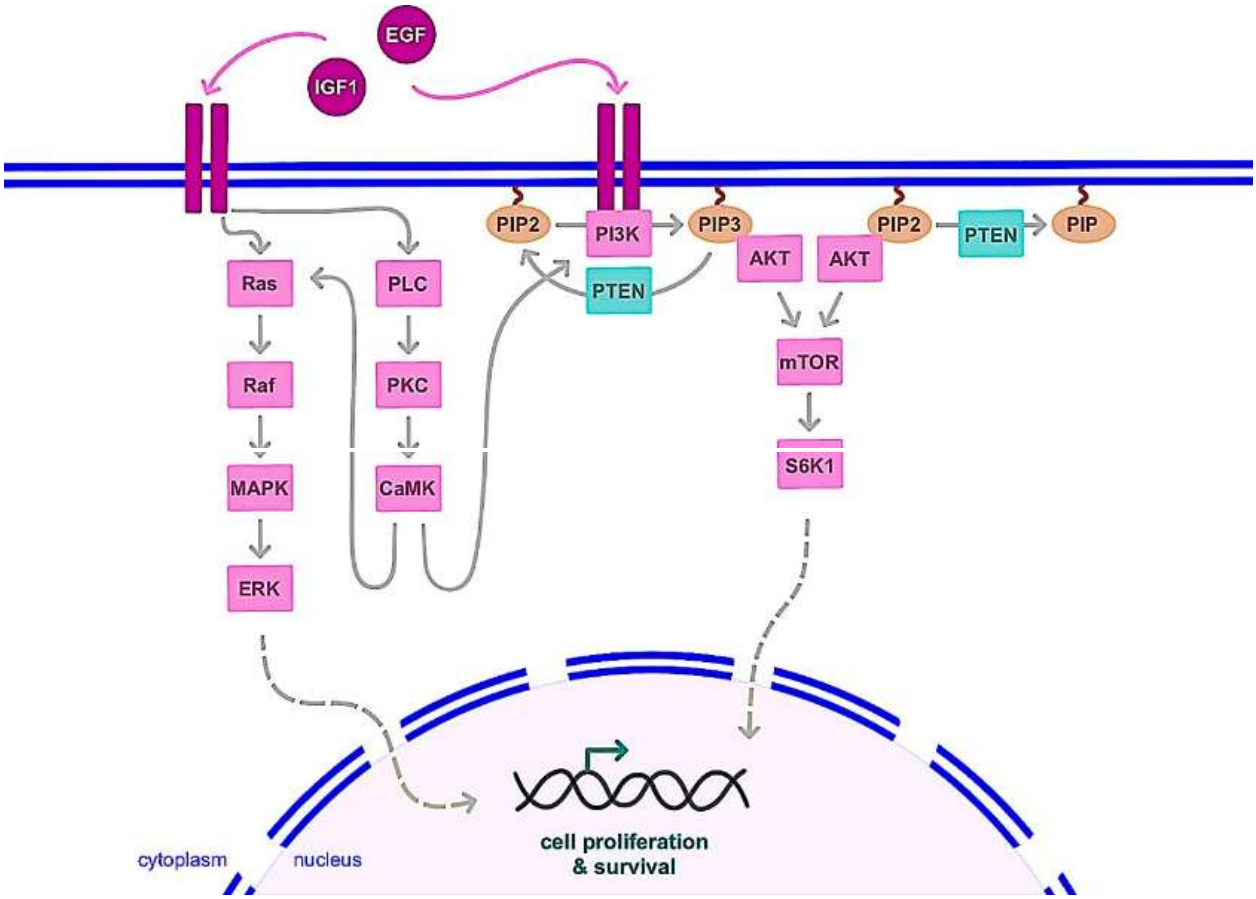

Figure 2. Signaling pathways activated by growth factor receptors promote cell proliferation and survival.

Figure 2 shows stimulation of growth factor receptors, such as EGF or IGF1, stimulates signaling pathways such as Ras/MAPK/ERK and PI3K/AKT/mTOR, which regulate cell destiny through transcription factor activation. PTEN inhibits PIP2 phosphorylation, which is required for PI3K-activated AKT. CaMK is a Ca2+/calmodulin-dependent protein kinase, EGF is epidermal growth factor, IGF1 is insulin-like growth factor 1, MAPK is a mitogen-activated protein kinase, mTOR is mammalian target of rapamycin, PI3K is phosphoinositide 3-kinase, PIP is phosphatidylinositol phosphate, PKC is protein kinase C, PLC is phospholipase C, PTEN is phosphatase and tensin homolog, and S6K1 is a transcription factor.

2.3. Diagnosis and Treatments

Clinical examination, imaging, and biopsy analysis are used to make the initial diagnosis of breast cancer. The pathological examination of the biopsy includes a systematic evaluation of prognostic and predictive factors like tumor size, histoprognostic grade Scarff-Bloom-Richardson I to III, mitotic index or Ki67, evaluation of ER and PR status, and the search for HER2 amplification. Up to 75% of patients have ductal carcinoma, while the remaining patients have lobular carcinoma (10–15%) and mixed ductal/lobular carcinoma. In the United States, at the time of diagnosis, over 60% of breast tumors are located in the breast, nearly 30% have spread to regional lymph nodes, and 5–10% of tumors are classified as metastatic [40].

Furthermore, it is noteworthy that luminal White women are most likely to get breast cancer (67%), followed by premenopausal white women (57%), African American women (55%), and premenopausal African American women 40% [41]. Various treatment options are available and are combined based on the characteristics of each patient once the kind and stage of breast cancer have been determined.

Breast cancer is typically treated with (i) surgery, which removes the tumor while preserving the mammary gland as much as possible in 75% of cases; (ii) radiotherapy, which is a targeted irradiation intended to destroy any remaining tumor cells after surgical treatment; (iii) chemotherapy, such as anthracycline and taxane, which are frequently used in HER2 amplified and triple-negative tumors and represent a non-targeted treatment that destroys dividing cells and can be administered before surgery to reduce the tumor's size and/or after surgery if there is a high risk of relapse [40–42].

(iv) hormone therapy, a specific treatment for luminal breast cancer that mainly consists of lowering estrogen levels in postmenopausal women or applying estrogen receptor antagonists to premenopausal women; (v) other specific treatments, like blocking the PI3K-AKT-mTOR pathway, which is essential for hormonal escape and is involved in cell proliferation and survival, or targeting HER2 with the monoclonal antibody trotuzumab (Herceptin) [43]. Additionally, neoadjuvant endocrine treatment is becoming in significance. Notably, individuals with metastatic ER+/HER2- have been seen to benefit from the combination of endocrine treatment with CDK4/6 inhibitors, which operate at the cell cycle level [44,45]. As a result, all of these therapies considerably increase patient survival [42–46].

To confirm the absence of recurrence, modify therapeutic care, and guarantee the effectiveness of the selected treatment, patient follow-up—typically by imaging—is crucial. Another tactic created in recent years is the study of circulating tumor DNA to determine the best course of treatment for each patient based on the course of her cancer. Oncogenic mutations can be found using this non-invasive technique, and their existence can direct therapeutic management toward the selection of certain medications [47]. In fact, 83% of the tissue from metastatic tumors had a PIK3CA mutation [48].

The usefulness of methylation signatures as non-invasive liquid biopsy indicators for breast cancer detection is demonstrated by the differentiating methylation areas at the genome level between normal breast tissue and triple-negative breast cancer tissue [49]. It is also possible to identify circulating tumor cells in the blood and use them as a biomarker to determine whether or not treatment for metastatic cancer is effective [50]. However, before these strategies can be used on a regular basis, their effectiveness must be confirmed by more clinical research.

RESULTS AND DISCUSSION

ER-Positive Breast Cancer

With tumor cells known as luminal A and B that express the ER, hormone-dependent breast cancer affects about 70% of patients. Estrogens are the main signals that contribute significantly to the development and spread of tumor cells in these

malignancies. The nuclear ER, ER, and membrane G protein-coupled ER (GPER, also known as GPR30) are the main mechanisms via which estrogens act in cells. Since the ER is thought to be the receptor primarily implicated in the genesis of breast cancer [8], it is a crucial target for treatment of breast cancer.

3.1. Molecular Mechanism of ER

3.1.1. Genomic Action

The transcription factor ER controls the expression of genes related to death, proliferation, and cell cycles. In fact, ER activation permits the production of oncogenic factors such MYC, Cyclin D1, FOXM1, GREB1, BCL2 or amphiregulin, IGF-1, and CXCL12, which raise the likelihood of DNA damage in response to estrogens and the proliferation of cancer cells [9]. Following its binding to the ER, estrogen (E2) enables the receptor to dimerize, translocate to the nucleus, alter its conformation to an active state, and engage with transcriptional coactivators (Figure 3). It is noteworthy that, in contrast to E2, antagonistic compounds like tamoxifen cause the ER to adopt an inactive conformation, which attracts transcriptional corepressors [51].

After then, ligand-activated ER attaches itself to estrogen-responsive elements (EREs) found in target gene promoters. Through serum responsive elements (SREs), ER can also interact with transcription factors, including activator protein 1 (AP1) and specific protein 1 (SP1), to control genes whose promoters do not include ERE (Figure 3). Thus, hundreds of target genes involved in cell growth and differentiation have their transcription controlled by this chromosomal activity [52–54]. The majority of breast cancers, referred to as ER+ or luminal, originate primarily as a result of the dysregulation of ER expression, activity, or its coregulators and target genes. It should be mentioned that estrogens have the ability to stimulate the two additional receptors, ER and GPER. ER is a nuclear receptor that is similar to ER and is encoded by the ESR2 gene and with a structure similar to ER [55].

Similar to ER~, ER} is expressed in a variety of non-reproductive organs such the brain, lungs, adrenal glands, and adipose tissue, as well as several reproductive organs like mammary epithelial cells, ovaries, uterus, and testes. With varying affinities, this receptor interacts with several ER transcriptional coregulators and shares ligands with ER, including estrogens and selective estrogen receptor modulators (SERMs). Activating ER, as opposed to ER, often causes apoptosis and reduction of proliferation; however, these outcomes vary depending on the tissue under investigation, the cell environment, transcriptional coactivators, and whether ER is coexpressed [55].

A positive prognosis is thus often associated with ER expression in breast carcinoma cells, however some research suggests the contrary. In fact, prior research suggests that ER and its isoforms, together with certain coactivators including AIB1, NF-kB, and TIF-2, tend to coregulate the growth and spread of breast cancer cells [56,57]. These particular coactivators were linked to high ER expression in high-grade breast tumor subtypes and are linked to poor clinical outcomes, which suggests that they may promote ER proliferation in breast cancer cells [58]. Therefore, more research is required

to fully comprehend this receptor's physiological function and how it relates to breast cancer [59,60].

There have been reports of both ligand-dependent and -independent ER activation [61,62]. The stability, dimerization, subcellular localization, DNA binding, and interaction with cofactors of ligand-independent ER are all impacted by the many post-translational modifications that target ER [63]. One important way of ligand-independent activation of ER is specifically phosphorylation of ER when growth factors activate certain intracellular kinases [64–66]. Notably, phosphorylation of tyrosine 537 (Tyr537), serine residues 118 (S118), S167, and S305 enhances ER activity in breast cancer cells via interacting with coactivators [66–71]. The acetylase p300 also acetylates ER at several lysine residues. Remarkably, acetylation of lysine 302/303 decreases ER activity, whereas acetylation of lysine 266/268 increases ER transcriptional activity [72].

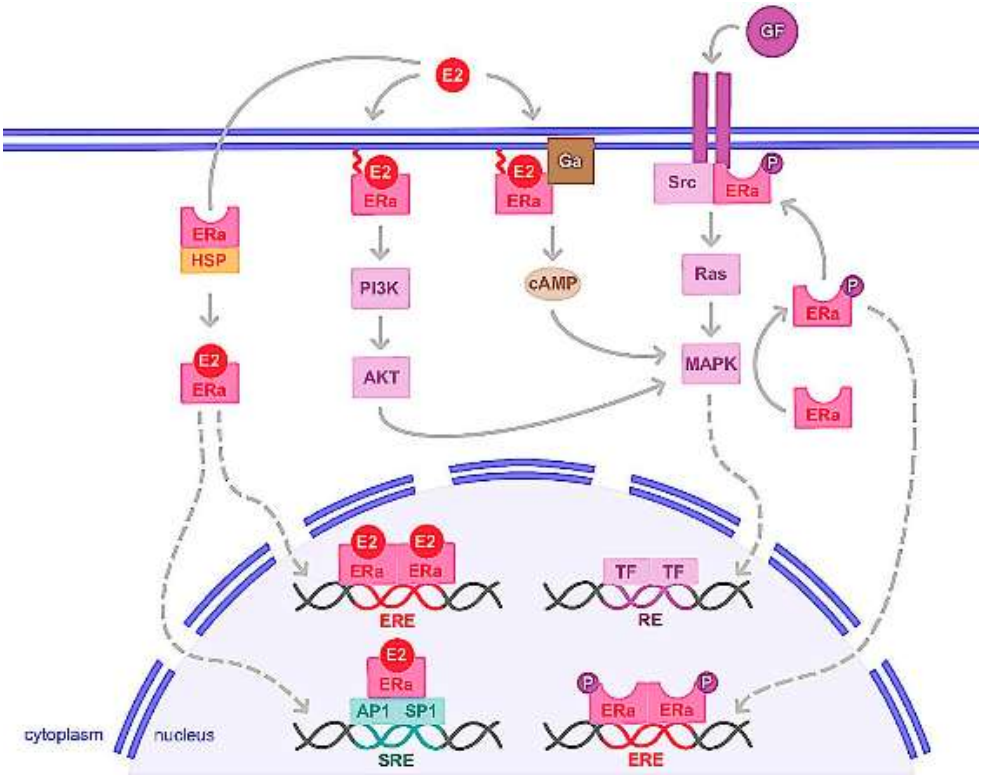

Figure 3 Estrogen Receptor Alpha (ERα) Signaling Pathways in Breast Cancer: Genomic and Non-Genomic Actions

Figure 3 shows after growth factor (GF) receptor activation, cellular kinases phosphorylate (P), which causes it to go into the nucleus. When the ERα homodimer binds to other transcription factors like AP1 or SP1, which bind DNA through serum responsive elements (SREs), it may also bind DNA directly or indirectly through estrogen responsive elements (EREs). This is the so-called genomic action of ERα, which results in target gene transcription regulation. Additionally, ERα can interact with GF receptors or G proteins (Ga) while being membrane-anchored. ERα activation is subsequently linked to the synthesis of second messengers (cyclic adenosine monophosphate, or cAMP) and the stimulation of signaling pathways, such as Ras/MAPK or PI3K/AKT. ERα's

nongenomic action ultimately triggers the activation of transcription factors (TFs), which control cell survival and proliferation. HSP: heat shock protein; MAPK: mitogen-activated protein kinase; P: phosphate; PI3K: phosphoinositide 3-kinase; E2: estrogen; ERα: estrogen receptor alpha; ERE: estrogen responsive element; Ga: G alpha protein; GF: growth factor; cAMP: cyclic adenosine monophosphate; and SRE: serum responsive element.

3.1.2. Nongenomic Action

Previous studies have examined the interaction between sex steroid (androgen or estrogen) signaling and growth factors like EGF or IGF at various levels [73,74]. Indeed, a tiny fraction of cytosolic or membrane-anchored ERα also quickly and momentarily exerts non-genomic activity in addition to its translocation into the nucleus and its role as a transcription factor for genomic pathways [75,76]. This includes cAMP (cyclic adenosine monophosphate) and other intracellular signaling pathways being quickly activated.

This entails the quick activation of intracellular signaling pathways, such as the PI3K/AKT, Ras/MAPK, or growth factor receptors, or the synthesis of cAMP (cyclic adenosine monophosphate) (Figure 3). The MAPK is activated when E2 binds to the ER, which quickly forms a cytoplasmic complex with many proteins, including the p85 subunit of PI3K and the Src protein kinase. and Akt pathways following ligand interaction for about 2 to 15 minutes [77–79].

Posttranslational alterations serve as the foundation for the processes by which ER targets the plasma membrane and its non-genomic activity. For instance, the human ER's cysteine 447 must be palmitoylated. When palmitate binds to this residue, the receptor becomes more hydrophobic and can attach to the caveolae, which are areas of the plasma membrane that are rich in cholesterol [80]. It's interesting to note that this interaction between ER and caveolin-1 in the plasma membrane sets off non-genomic signaling pathways, cyclin D1 activation, and cell division [80–82]. Additionally, Le romancer and colleagues [83] shown that the interaction of ER with Src and p85 partners, and therefore the stability of the estrogen-induced ER/Src/p85 complex, depend on the arginine methyltransferase PRMT1 methylating ER on arginine 260. Furthermore, ER methylation, ER/Src/p85 interaction, and downstream Akt activation all depend on Src and PI3K activity [63,84,85]. Notably, ER methylation only takes place 5–15 minutes following ligand stimulation [63]. Additionally, take note of the fact that IGF-1 stimulates PRMT1 to rapidly methylate ER, which in turn promotes ER to bind to the IGF-1 receptor in MCF-7 breast cancer cells. It's interesting to note that in a cohort of breast cancers, IGF-1 receptor expression was favorably connected with the ER/Src and ER/PI3K interaction [84,85].

However, phosphorylation of ER's Tyr537 is essential for ER's interaction with Src kinase, MAPK pathway activation, and cell proliferation [86]. In addition to the mammary gland, other organs including the liver and adipose tissue also produce GPER, a seven transmembrane domain protein that can cause fast cellular effects of estrogen [87, 88]. A number of breast cancer cell types have also been shown to express GPER [89].

When estrogen stimulates it, cAMP levels rise and intracellular calcium is mobilized [90,91].

Additionally, this leads to the activation of signaling cascades including Ras/MAPK and PI3K/AKT, which in turn control the transcription of genes necessary for cell survival and proliferation [92,93]. These genes, which support cell proliferation and are involved in the cell cycle, include c-fos and cyclins D, B, and A. GPER induces them, but GPER downregulates other genes implicated in cell death, including BAX, caspase 3, and BCL2 [94–97]. GPER activation promotes tumor development and the production of HIF1, VEGF, and the endothelial marker CD34 in a mouse xenograft model of breast cancer [98]. The application of a GPER suppressing peptide, on the other hand, causes apoptosis and significantly reduces the growth of triple-negative mammary tumors in mice in this paradigm [99].

Since SERMs function as agonists of the membrane receptor GPER, activation of this receptor would thus seem to have a pro-tumor impact and may contribute to the development of resistance to hormone treatment [100–102]. Actually, by promoting the expression of genes implicated in breast carcinogenesis, tamoxifen has an agonistic impact [100,103]. Furthermore, there was a clear correlation between the existence of GPER and a worse relapse-free survival rate in ER-positive patients undergoing tamoxifen therapy [96,98]. To further understand the roles of the ER receptor and explore it as a potential treatment target for breast cancer, more research is necessary [104].

Except for a distinct 27-amino acid sequence that replaces the last 138 amino acids in the C-terminus of ER-46 and ER-66, the general structure of ER-36 is the same as that of ER-46. The actions of the two shortened isoforms, ER~46 and ER~36, differ somewhat from those of the traditional ER~66, particularly in the areas of ligand binding, transactivation, coregulator interaction, and subcellular localization [113,117,120]. Specifically, both ER-positive and ER-negative breast cancer cells express ER36, which is mostly found in the cytoplasm and at the plasma membrane [112,116,120].

The ER membrane-initiated and nuclear processes shouldn't be entirely separated. It is possible for genomic and non-genomic processes to communicate with one another. Phosphorylation of ER or its cofactors is one way that these two main ER pathways are related [105–107]. For instance, MAPK activity and the creation of an ER/Src/PI3K complex are necessary for E2-mediated transcriptional activation of cyclin D1 via the AP-1 binding site [106,107], suggesting that genomic and non-genomic signaling on E2 target genes are convergent [108]. Nonetheless, prior research has indicated that ER's non-genomic activity could be linked to endocrine treatment resistance and a poor prognosis for breast cancer [84,109,110].

Additionally, we demonstrated that as cancer progresses, ER's genomic activity decreases and its non-genomic activity increases as it transitions to the monomeric form [111].

3.2. ER*a* Variants and Mutations

Two significant lower molecular weight variations of ER, ER 46 kDa and ER 36 kDa, have been discovered in addition to the full-length ER, which is a 66 kDa protein [112–117].

These alternative splicing-derived variations have been found in both malignant and healthy breast tissues, as well as in a number of cell lines related to breast cancer [116,118,119]. While the ER36 isoform loses both transactivation domains, AF-1 and AF-2, but retains the DNA-binding domain and a portion of the ligand-binding domains, the ER46 isoform only differs from the full-length ER66 in the absence of the N-terminal activation function 1 (AF-1) [112,116].

Except for a distinct 27-amino acid sequence that replaces the last 138 amino acids in the C-terminus of ER-46 and ER-66, the general structure of ER-36 is the same as that of ER-46. The actions of the two shortened isoforms, ER~46 and ER~36, differ somewhat from those of the traditional ER~66, particularly in the areas of ligand binding, transactivation, coregulator interaction, and subcellular localization [113,117,120]. Specifically, both ER-positive and ER-negative breast cancer cells express ER36, which is mostly found in the cytoplasm and at the plasma membrane [112,116,120].

Additionally capable of binding to DNA, this receptor suppresses ER66's genomic activity. When estrogens are present, it exhibits non-genomic action in the cytoplasm, enabling the activation of many pathways, most notably the MAPK pathway, which fuels the aggressiveness and spread of cancer. Additionally, ER36 can cause resistance to antiestrogens and modulate the agonistic effects of tamoxifen [121–125].

To completely understand the biological functions of these ER variations and ascertain if they represent a viable therapeutic target, more investigation is necessary. It is also noteworthy that information on diagnostic and therapy options depends on the assessment of ER status in breast cancers. Nevertheless, the existing immunohistochemistry (IHC) analytical techniques have drawbacks and are unable to distinguish between different ER subtypes in the biopsies. Therefore, unique antibodies for each of these isoforms are necessary for accurate characterisation of these variations.

According to earlier research, ER gene mutations account for fewer than 5% of original tumors, but they can rise to 50% in metastatic resistant cancers, particularly in patients using aromatase inhibitors (AIs) [126]. To date, 62 ER gene mutations have been identified in tumor samples. The ER ligand-binding domain (LBD) has the majority of these alterations (47 out of 62), and some of them render the receptor constitutively active [127].

This implies that the selective pressure of AI medication and, consequently, estrogen deprivation is the only factor that causes these ER activating alterations. The two most prevalent ER mutations identified in malignancies are Y537S and D538G. The significance of these mutations in the resistance to endocrine therapies is demonstrated by the fact that they cause the receptor to remain in its active conformation in the absence of a ligand, improve coactivator interactions with the receptor, and significantly reduce its affinity for antiestrogens, tamoxifen, and fulvestrant. A recent work on breast cancer cells is also noteworthy since it shown that these ER mutations cause the epithelial-

mesenchymal transition and encourage the growth and invasion of cancer cells both in vivo and in vitro [128].

3.3. Hormone Therapy and Resistance

Hormone therapy is the preferred treatment since estrogen activation of the ER is required for two-thirds of breast cancer cell growth. In order to prevent breast cancer from recurring and to improve patient survival overall, this involves either denying the tumor estrogen or inhibiting ER function. The most well-characterized and frequently used ER antagonist is tamoxifen, a member of the SERM family [129]. In contrast to estrogen, tamoxifen's binding to the ER results in the recruitment of corepressors, which encourages the suppression of breast cancer cell proliferation [130].

The preferred course of therapy for premenopausal and postmenopausal women is a 5-year regimen of tamoxifen. For almost two decades, tamoxifen has been the sole medication available for advanced breast cancer. But the advancement of AIs in the late 1990s drastically changed first- and second-line therapies. These medicinally effective active ingredients (letrozole, anastrozole, or exemestane) prevent the enzyme aromatase from converting androgens into estrogens [131].

In fact, although the ovaries create the majority of estrogen in premenopausal women, aromatase, which is found in tissues other than the ovaries, such as adipocyte and breast tissues, can cause estrogen production in postmenopausal women, which may promote the growth of tumors [131]. With the development of the ER antagonist fullvestrant in the early 2000s, a new class of medicinally active compounds was created. SERDs (selective estrogen receptor degraders) are members of this class; they attach to ER and degrade it, inactivating it [132]. In contrast, SERMs modify the conformation of ER by encouraging the recruitment of co-repressors [129]. Fulvestrant has the same binding affinity to the ER as E2 in the absence of agonist action. Fulvestrant is typically only used to treat luminal metastatic breast cancer, or for patients who have become resistant to a first hormone therapy with IAs or SERMs [133].

In postmenopausal women with advanced malignancies, fulvestrant is administered intramuscularly. On the other hand, novel oral SERDs are presently being created and evaluated in clinical studies [134]. Breast tumor cells may evade hormonal regulation in around 30% of ER+ breast tumors, giving them the capacity to multiply without the stimulation of estrogen. The loss of the epithelial phenotype and the acquisition of a more migratory and invasive capability are commonly observed in conjunction with hormonal escape [135].

In postmenopausal women with advanced malignancies, fulvestrant is administered intramuscularly. On the other hand, novel oral SERDs are presently being created and evaluated in clinical studies [134]. At that point, hormone treatment loses its ability to stop the growth of cancer. Only 10% of cases of this resistance are caused by a decrease in ER expression; instead, it results from a dysregulation of this receptor's activation, which can be triggered without the presence of estrogen. This ligand-independent activity can result from a variety of mechanisms, but the most common ones are (i) mutations that make ER constitutively active; (ii) epigenomic and post-

translational changes in the ER; (iii) activation of ER by oncogenic intracellular signaling pathways like PI3K/AKT and Ras/MAPK as well as growth factors (EGFR, HER2, IGF1R, and FGFR), which are also deregulated in cancer cells; and (iv) an increase in ER interaction with coactivators at the expense of its corepressors [135].

In fact, poor clinical outcomes and an adverse response to tamoxifen are predicted by low expression of corepressors such NCOR1 or high expression of coactivators like AIB1 [58,61]. One treatment strategy for individuals who have developed resistance is to focus on the signaling pathways that contribute to ligand-independent ER activation. For instance, ER-positive breast cancer frequently exhibits abnormalities of the PI3K/AKT pathway, which may be essential for tumor resistance. Thus, alpelisib and everolimus, which are inhibitors of the PI3K/AKT pathway, can be used in conjunction with hormone treatment [43].

Hormone treatment may also be used in conjunction with CDK4/6 inhibitors like palbociclib and ribociclib or with histone deacetylase (HDAC) inhibitors like vorinostat and entinostat [44,136–139]. In fact, CDK4/6 and ER activations as well as cell cycle progression are caused by overexpression of cyclin D1, which is seen in 50% of breast tumors [140]. ER-positive metastatic breast cancer is now commonly treated with CDK4/6 inhibitors in conjunction with hormone treatments [141]. It is also noteworthy that histone acetylation and DNA methylation are probably the most prevalent epigenetic alterations that occur when cancer progresses. Endocrine-resistant ER+ breast cancer may be re-sensitized by DNA demethylating agents such decitabine, 5-azacytidine, and HDAC inhibitors [142,143].

Furthermore, via boosting immunocompetent monocytes, the HDAC inhibitor entinostat also has immunomodulatory effect, increasing overall lifespan [144]. Moreover, clinical trials are being conducted to evaluate the effectiveness of various treatment combinations based on the characteristics of each patient [145]. Lastly, it should be mentioned that stem cells have ER and other steroid receptors, which may regulate the actions of cancer stem cells that contribute to tumor recurrence and treatment resistance [146].

CONCLUSION

Fundamental Finding : This review underscores the pivotal role of estrogen receptor (ER) signaling in the pathogenesis and progression of hormone-dependent breast cancer, highlighting both genomic and non-genomic pathways, as well as emerging evidence of ER's function as an RNA-binding protein that enhances tumor adaptability. **Implication :** A deeper understanding of ER signaling mechanisms provides valuable insight into the development of therapeutic resistance and supports the rationale for targeting ER-associated molecular alterations in endocrine-resistant breast cancer. **Limitation :** However, the complexity and heterogeneity of ER+ tumors, along with incomplete knowledge of non-genomic pathways and epigenetic influences, remain significant challenges in fully elucidating ER function. **Future Research :** Further investigations are warranted to explore the dynamic interactions of ER with

transcriptional machinery and intracellular signaling networks, as well as the development of novel agents—including epigenetic drugs and combination therapies—to overcome resistance and improve clinical outcomes in ER+ breast cancer.

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* **Ali Abbas Sadiq Alqaisi (Corresponding Author)**
Diyala University, Iraq

Hawraa Haider Abbas Jasim
Alqasim Qreen University, Iraq

Areej Haider Saleh
Alqasim Qreen University, Iraq

Rafal Ayad Kazem
Alqasim Qreen University, Iraq

Afnan Abbas Fadhel
Alqasim Qreen University, Iraq

Saja Ali Kashkul
Alqasim Qreen University, Iraq