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Review Article

The Estrogen Receptor and Breast Cancer: A Complete Review

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Abstract

Estrogens play an important role in normal breast development as well as breast cancer progression. Most of the effects of estrogen are mediated through its two receptors: estrogen receptor α (ERα) and β (ERβ). Both ERα and ERβ are intracellular nuclear hormone receptors and mediate estrogen signaling primarily through transcriptional activation of target genes. Estrogen is an essential hormone for mammary gland development and reproductive organ function. Estrogen also regulates other diverse physiological functions associated with the cardiovascular, central nervous, immune, and skeletal systems. This review will summarize the current body of knowledge on ERα and ERβ in cancer. Clinical correlations between estrogen receptors have also been reported. Thus, this review will discuss the estrogen receptors signaling pathways.

1. Introduction

One of the most common forms of cancer that affects women in industrialized countries is the breast cancer. More than 1.3 million women around the world are diagnosed with breast cancer [1]. Increasing sensitivity or longer exposure to estrogens, endogenous estrogens are thought to be greatly involved in the breast cancer [2].

In the USA, the incidence and mortality in 2018 were 268 670 and 62 330, respectively. In 2019, although the incidence in the USA increased to 271 270 in 2019, the estimated breast cancer mortality was reduced to 42 260. In the UK the incidence is around 55 200 with approximately 11 400 breast cancer deaths [3]. The methods to prevent breast cancer are are in great importance, therefore recognizing the existence of tumor and the type of cancerous tumor would have a very important role on getting decision for applying the methods of true treatment [4][5].
In terms of structure and function there are two subtypes of ER, ERα and ERβ [6]. ERα-mediated metastasis of breast cancer could be impaired by ERβ, indicating that ERβ acts as a tumor suppressor, so a higher expression level of ERβ could be a good prognostic marker for ERα+ breast cancerc[7]. Two major female sex hormones, the steroid hormones 17β-estradiol (E2) and progesterone (P4),

Development of the mammary glands and the reproductive system and brain, skin, and bone homeostasis essentially depend on E2 . The estrogen receptor α (ERα) is expressed in More than 70% of all human breast cancers which are E2 dependent for growth., translocation of liganded ERα into the nucleus and its recruitment to chromatin through multiple mechanisms occurs upon E2 stimulation , including binding to a cognate DNA sequence known as estrogen response elements (EREs)c[8].

Estrogen hormone plays an essential role in mammary gland development and reproductive organ function. Estrogen also functions as a regulatory element in diverse physiological processes in the cardiovascular, central nervous, immune, and skeletal systems. Estrogen exerts its effects via estrogen receptors (ER), including ERα and ERβ. Both ERα and ERβ are located in the nucleus through which Estrogen primarily activates transcription of target genes. Estrogen-driven proliferation of the normal breast in puberty and breast cancers is mediated by ERα, however, anti-proliferative effect of ERβ on the normal breast has been shown. Deregulated ERα expression and signaling in cell proliferation, survival, and migration can induce tumors in estrogen-regulated tissues such as the breast, endometrium

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and colon. ERα is expressed in 70 % of the breast cancers and as it is estrogen receptor positive (ER-positive), ER-positive breast cancer patients are treated with an anti-estrogen, such as tamoxifen [6][10].

According to immunohistochemical staining of estrogen receptor α (ERα), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), breast cancer is categorized into the following groups; Luminal, subtype A: ERα+/PR+/ HER2-; luminal, subtype B: ERα+/PR+/HER2+; HER2 overexpression: ERα-/PR-/HER2+ and triple-negative breast cancer (TNBC): ERα-/PR-/HER2-[10].
Triple negative breast cancers (TNBC) comprise ten to twenty percent of all breast cancers [1].

Estrogen receptor alpha (ERα) and progesterone receptor (PR) are not expressed in this breast cnacer subgroup and human epidermal growth factor receptor 2 (HER2) is not also amplified. TNBCs are more frequently found in younger patients and tumors are generally larger in size. Aggressiveness of TNBCs and its high grade often involve lymph node at diagnosis [11][12].

NH white women had the highest incidence rate of the HR+/HER2− subtype, and NH black women had the highest rate of the triple-negative subtype. Compared with women with the HR+/HER2− subtype, triple-negative patients were more likely to be NH black and Hispanic; HR+/HER2+ patients were more likely to be NH API; and HR−/HER2+ patients were more likely to be NH black, NH API, and Hispanic. program. This article presents the first report of nationally representative incidence rates for the major breast cancer subtypes based on joint ER/PR/HER2 status and an assessment of demographic and clinical differences across these subtypes using SEER data covering an estimated 28% of the US population [13].

The most common breast cancer subtype which comprises 80% of all patients are Estrogen receptor positive (ERþ). Standard advanced ERþ breast cancer therapy includes endocrine therapies, such as selective ER modulators, selective ER downregulators and estrogen suppression with aromatase inhibitors. The efficacy of these therapies in preventing metastatic recurrence have been proven by randomized clinical trials. Data show recurrence of the cancer in 20 % of the patients with operable ERþ tumors during or after adjuvant endocrine treatment. Despite the effectiveness of these treatments, the frequency of annual breast cancer deaths from antiestrogen-resistant ERþ tumors is still at a very high rate. Quinazolinones-based compounds have ability to suppress prostate tumor growth via apoptosis [14]. Up to now, the only mechanisms of antiestrogen resistance that are supported in the clinic are HER2 amplification (3, 4), mutations in the ligand-binding domain (LBD) of ESR1 (5, 6), and dysregulation of the CDK4/6 pathway [15].

RNA sequencing (RNA-seq) detects estrogen receptor alpha gene (ESR1) fusion transcripts in estrogen receptor-positive (ER+) breast cancer. This study demonstrated that two in-frame ESR1 fusions in a small late-stage cohort of metastatic ER+ cases drive not only endocrine therapy resistance but also metastatic disease progression [16].

ER is a transcription factor consisting of various functional domains encoded by ESR1 located on chromosome 6. ESR1 transcripts are generated by 2 non-coding and 8 exons that specifies protein-coding domains. The N-terminal activation function 1 (AF1) domain functions in a hormone-independent manner and is post-translationally modified by phosphorylation events that increase transcriptional and pathogenic activity [17].

2. The Estrogen Receptor Signaling Pathways

Two types of estrogen receptors (ERs1), alpha and beta have been recognized. Both ERα and ERβ produce a protein product from a separate gene located on different chromosomes but share 97% identity in their DNA binding domains and 55% identity in their ligand-binding domains[6] , and as Class I members of the nuclear hormone receptor superfamily, are composed of the following six functional domains, labeled A-F: (I) the N-terminal A/B domain; (II) the C domain containing the DNA-binding domain (DBD1); (III) the D domain possessing signals for nuclear localization; (IV) the E domain, or the ligand binding domain (LBD1); (V) the C-terminal F domain, which is unique to the ERs among the nuclear receptors and not well conserved; and (VI) the N-terminal domain of the ER, which contains a ligand-independent activation function (AF1)-1 that appears to be more important in ERα than ERβ.

The two zinc finger structures in the DBD play a great part in binding the receptors to estrogen response elements (EREs1) sequence within the regulatory sequences of target genes. The DBD for ERα and ERβ are 97% homologous and are highly likely to bind to the same EREs

The ligand binding and receptor dimerization are mediated by E, and ligand specificity and transactivation of target gene expression via the AF-2 domain are readily established. the ligand-dependent transactivational activity and recruitment of coregulator proteins are essentially dependent on The AF-2 domain [18].

Several splice variants have been described for both receptor subtypes. The coding sequence is similar in most ERα, however, 5-untranslated region (UTR) is different. Exon 1 doesn't not exit in shorter ERα isoforms, and thus the NH2-terminal AF-1 (here termed hERα-46 and hERα-36) is isolated and identifies in differet cell lines.

Unlike ERα, several splice variants of ERβ are expressed in tissues. The 530-amino acid (aa)-long human ERβ isoform is currently regarded as the wild-type ERβ (rat and mouse, 549 aa) (140). Many of the ERβ isoforms are expressed as proteins in tissues [19].

these Upon binding estrogen, activation of target gene transcription and cell growth occurs by ER either directly through its genomic pathway or indirectly through nongenomic pathway that involves the PI3K/AKT pathway. Cancer cell proliferation or apoptosis resistance is readily promoted due to the oncogenic nature of most of the well-characterized ER-target genes ; for example, cyclin D1, antiapoptotic Bcl2, and pS2.[20] ER-α expression is inversely correlated with with epidermal growth factor receptor (EGFR) in human breast cancer.

A study showed omitting estrogen from the growth media led to overexpression of EGFR by MCF7 cells which indicates ER-α can be a growth inhibitor under some circumstances. Two different pieces of evidence showed how proliferation in breast cancer cells is stimulated by ER-

α [11]. First, ER-α targets the components of the IGF-I signaling pathway, and cells that lack ER-α expression will lack IGF-I signaling pathway as well[21].

Recent work from large consortial studies led to the discovery of novel breast cancer susceptibility loci in genic (CASP8, FGFR2, TNRC9, MAP3K1, LSP1) and non-genic regions (8q24, 2q35, 5p12) of the genome, and has demonstrated substantial heterogeneity by tumor characteristics. In particular, susceptibility loci in FGFR2, TNRC9, 8q24, 2q35, 5p12 have stronger associations for estrogen receptor positive disease (ER +) than estrogen receptor negative disease (ER −). These findings indicate that common genetic variants can exert influence on the pathological subtype of breast cancer, and provide further support for the hypothesis that ER+ and ER− disease result from different etiologic pathways (Garcia-Closas and Chanock 2008).

Combination of Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors with endocrine therapy is used to treat hormone receptor–positive, HER2-negative breast cancer [22].

How hormones regulate gene transcription and chromatin architecture.

The hierarchical events occurring at the genomic and epigenetic level in exposure to estrogens are poorly understood. In ER+ breast cancer cells, after ERα recruitment to chromatin and being ubiquitinated, it cycles on and off ERE sites to activate target gene transcription.

After ligand binding, recruitment of a number of ERα cofactors to chromatin occure in a tightly coordinated and dynamic manner. ERα-driven transcriptional activity resumes to occur for hoursafter being triggered by estrogen. A large proportion of these transcriptional changes is independent of chromatin accessibility, however, chromatin accessibility can also be required for recruitment of factors involved in gene repression [8].

Multiple promoters control the regulation of ERα transcription. To date, at least nine promoters have been discovered upstream of the translation start site of human ERα. It is previously has been proven that estrogen receptor promoter B associated factor 1 (ERBF-1) is essential for the transcription activity of a distal promoter (promoter B) in ERα-positive breast cancer cells.

Cells expressing ERα mRNA express ERBF-1 which is transcribed from promoter B and has a great role in the expression of the ERα gene in breast cancer. Transcription factors such as activating protein 1 (AP1) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) can modulate gene transcription through heterodimerizing with ERα. Genes such as pS2, cathepsin D, c-fos, c-jun, c-myc, TGF-α, retinoic acid receptor α1, efp, progesterone receptor (PR), insulin-like growth factor 1(IGF1) are responsive to estrogen [16].

2.1. ER Domain Mutated Mouse Models

Genetically modified estrogen receptor domains in mouse models are used to allow dissection of function of the ER domains.

These include models with altered DNA binding domains (NERKI and EAAE) which disrupt binding to the estrogen responsive DNA element, as well as one model with a point mutation in the ligand binding domain (ENERKI) which disrupts estradiol mediated transcription activation by inhibiting estradiol binding. Furthermore, mouse models have been made with the deletion of AF-1 or AF-2 (AF-10 and AF-20) and point mutations in the core AF-2 (AF2ERKI). In vitro experiments suggest that the AF-1 activity is necessary for the antagonist dependent AF2ER activation.

The EAAE mutant harbors amino acid exchanges at four positions of the DNA-binding domain (DBD) of ERα. This construct was knocked in the ERα gene locus to produce ERα (EAAE/EAAE) mice devoid of a functional ERα DBD. The phenotype of the ERα(EAAE/EAAE) mice resembles the general loss-of function phenotype of αER knockout mutant mice.

The initial gene targeting of ERα, consisting in the introduction of a Neo cassette in exon 2 [αERKO, hereafter called ERα-Neo KO (knockout)], was reported in 1993. More recently, another mouse deficient in ERα because of the deletion of exon 2 (ERαKO, hereafter called ERα-Δ2 KO) was generated.

Studies showed that ovariectomized ERα-WT mice treated with E2 presented a significant increase in uterine weight. ERα-Δ3 KO mice showed no increase under E2 treatment. ERα-Neo KO mice showed a significant increase in uterine weight, although only partial when compared with WT mice [23].

3. Estrogen Reseptor α

ER-α as the first receptor subtype to be identified in the breast, many studies have focused their attention on the biological functions of ER-α in the mammary gland. The results indicate that regulating events during the S and G2/M phases of the cell cycle in a ligand-dependent fashion, ERα can modulate breast cancer cell proliferation.

Estrogen receptor alpha (ERα) plays a pivotal role in hormonedependent cancer development and the status of ERα is used for designing treatment strategy and for prognosis. A closer look at the cross-talk between p53 and ERα has revealed that their activities are mutually regulated.

Human ERα is expressed as two main isoforms, ERα and ERα46, the latter of which lacks the N-terminal AF-1. ERα46 can form a heterodimer with full length ERα, resulting in suppression of ERα transactivation activity. A third ERα isoform, ERα36, which lacks both transactivation domains AF-1 and AF-2, has been identified. Unlike full length ERα and ERα46, ERα36 is localized in the cytoplasm and the plasma membrane, where it is thought to mediate non-genomic estrogen signaling.

Based on the rationale provided by the study results, a cell cycle inhibitor in combination with a drug that lowers estrogen levels, such as an aromatase inhibitor, and an antiestrogen that does not result in the degradation of ERa, such as tamoxifen are effective treatment options [25].

Liganded ERα is suggested to regulates gene expression through modifying enhancer-promoter interactions [25][26]. Enhancer-bound ERα play pivotal role in the expression of E2-induced genes [27][28]. Results indicate that after acute administration, typically minutes, of E2 and P4, induce massive alteration in gene transcription and chromatin accessibility [29][30].

4. Estrogen Reseptor β

Second estrogen receptor gene (ESR2) located on a different chromosome produces ERβ which is homologous of ERα in the DNA-binding domain (97%), and partly homologous to the ligand-binding domain (55%). Defining the expression pattern of ERβ in the normal human breast and in various stages of cancer could pave the way to understand understanding the role of ERβ in breast cancer. Epithelium of the breast expresses high levels of ERβ, however, mice deficient in ERβ show a normal mammary histology. Mammary gland development is highly dependent on ERβ as it mediates the terminal differentiation of the gland during pregnancy and lactation, and exerts and effect on intercellular junctions and proliferation.

demonstrated a role for ERβ in negatively regulating the estrogen-induced pro-proliferative actions of ERα. For example, if ERβ and ERα are co-expressed in a cancer cell, estradiol and phytoestrogens have been shown to reduce proliferation in breast and prostate cancer cell lines in vitro. Functional differentiation of various epithelial and nonepithelial cell types is regulated by ERβ.

ERβ-/- females show different trend before puberty and after puberty. They seem to have normal mammary histology with normal ductal outgrowth of the mammary gland anlage, however, mammary gland outgrowth is failed after puberty as corpora lutea are rare, little progesterone is produced in the ovaries and, in contrast to their WT littermates. This condition is treated by administration of progesterone to stimulate sde branching. Moreover, mammary glands of ERβ-/- mice is morphologically indistinguishable from those of their WT littermates [31].

Less proliferative ER signature, low ERα and high nuclear expression of ERβ in mice at low risk of breast cancer (parous mice) have been shown in one study. Determining the proliferative nature of the gland is highly dependent on the levels of both receptors within the normal breast epithelium which with developmental stages of oncogenic vulnerability could be predicted. [9]

ERβ2, The human ERβ variant, is suggested that it is normally expressed at higher levels than ERβ1 in breast cancers, and in contrast to ERβ1 it is linked with aggressive phenotypes of various cancers. Overexpression of ERβ2 has been seen in TNBC cells, while, on the contrary, cell proliferation and cell invasion was decreased in endogenous ERβ2 knockdown. Prolyl hydroxylase 3 (PHD3) gene expression decrease under the influence of ERβ2 is associated with hypoxia inducible factor 1α (HIF-1α) protein levels increase which is a potential mechanism for the invasive phenotype. The role of ERβ2 in enhancing cell proliferation and invasion is undeniable, beyond modulation of ERβ and ERβ1 signaling which might contribute to the invasive characteristics of TNBC [10].

Data in the first place show that ER β reduces the metastatic potential of TNBC cells. The expression of CXCR 4, an important pro‑metastatic factor, and cancer cell invasion are reduced with ER β agonists treatment. ER β agonists is a novel anti‑metastatic therapeutic approach that should be further investigated. [32]

It has been noted that ERβ can exert anti-proliferative effects in breast cancer cells in the presence of ERα, however, in the absence of ERα it increases proliferation. HC11 cell line is used to study ERa and ERb1 in cellular proliferation as are expressing both ERs. The ERa-selective agonist PPT could stimulate proliferation, whereas E2 did not exert any effects on it and more interestingly [33].

Most of ERβ effects is through binding to transcription factors other than ERE. In the study of the ERβcrispr−/− mouse MG, ERα and invasive epithelium were overexpressed. ERβ in ERβcrispr−/− mice play a key role in controlling growth and differentiation of the epithelium of MG and VP. [34]

As growth regulators in human breast cancer cells, Estrogen receptors (ERs) and the PTEN-Akt-mTor pathway are responsive to tamoxifen therapy. It is shown that tumor suppressor PTEN could maintain ERβ expression in breast cancer cells. [35]

Estrogen receptor β (ERβ) expression is reported in the most of invasive breast cancer cases, irrespective of their subtype, including triple-negative breast cancer (TNBC). It is thought that ERβ may be the probable target for therapy in this cancer type.

Because of tumor suppressive ability, decreased expression during carcinogenesis, increased proliferation in knockdown mammary epithelial and breast cancer cells is a great therapy target, however, tumor cell proliferation was inhibited its overexpression [36].

Being involved in breast cancer promotion, IGF-2is expressed in TNBC and neighboring cells in archival clinical specimens that upregulates ERβ mRNA in TNBC cells. ERβ suppression by the use of shRNA could significantly drive down TNBC proliferation. By promoting VEGF, amphiregulin, and Wnt-10b, ERβ can stimulate growth in the downstream which will activate signaling pathways linked with TNBC progression [37] .

Studies report ERβ expression in ductal cancer was significantly reduced in 80% of cells in normal tissue to very few in DCIS (Ductal carcinoma in situ and IDC). In all estrogen-dependent tumors ERβ expression has decreased from normal to tumor issue [38].

nd ligand. ERβ 1 is the ligand-binding form of ERβ variant isoforms. ERβ variant isoforms derive from alternatively spliced transcripts which contribute to C-terminally truncated proteins which have lost their ability to bind ligand [39].

5. Progesterone Receptor

ER+/PR- subgroup is not diagnosed properly as it is either different entity, or it signifies ERs because of their physiological effects on ER.

ERs physiologically induce PR synthesis. The two major proteins, isoform B(PRB) with high molecular weight and isoform A (PRA) that lacks the first 161 amino acids are coded by PR which are equally expressed in a normal mammary gland, however, the ratio is altered in tumors PRA dominating over PRB [40][41].

6. Conclusion

Estrogen has long been associated with breast cancer stimulation and anti-estrogen therapies such as tamoxifen are in great importance to block the growth and recurrence of hormonally responsive breast cancer. About 70% of breast

cancer patients are ER+ and can benefit from antiestrogen therapy. It has been shown that majority of the well characterized ER-target genes are oncogenic that could promote cancer cell proliferation and a large number of patients who have ER+ tumors are treated with tamoxifen for prevention of disease relapse and metastasis. As a direction for future work, we will utilize some machine learning [42-46] and neural networks based techniques [47-49] to be integrated with the developed method.

Conflict of Interest Statement

The authors declare no conflict of interest.

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