Review Article

A review on the role of estrogen, estrogen receptor and signaling pathways in breast carcinogenesis

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ABSTRACT

Estrogens were one of the primary female sex hormones, and it plays an important role in both reproductive and non-reproductive systems. It can also be synthesized in non-reproductive tissue as liver, heart, muscle, bone, and brain. The estradiol (E2) was considered to be a major estrogen hormone which is involved in the progression of breast cancer, and a majority of the human breast cancers start out as estrogen dependent and express the estrogen receptor (ER). Interruption of ER function mainly (ER)-α in breast cancer is an effective therapeutic strategy. HOXB13, IL17BR, and CHDH are estrogen-regulated genes where their prognostic utility is likely to impact on their regulation through both ER- and HER2-dependent pathways. Genomic and extranuclear signaling pathways are the main two estrogen signaling pathway where estradiol acts on the ER. In the genomic pathway, estradiol (E2) binds to ER-α and relocalizes estrogen to estrogen-responsive elements and promotes target genes expression. In the extranuclear signaling pathways, rapid E2 signaling activates PI3K/Akt/mTOR and eRK/mitogen-activating protein kinase pathway. Thus, estrogen signal regulates cell proliferation, apoptosis, and cell cycle, following control cell or tissue growth.

KEY WORDS: Estradiol, Estrogen, Estrogen receptor, Genomic and extranuclear signaling pathway

INTRODUCTION

Breast cancer is a heterogeneous disease, with genotypic and phenotypic variations and hormone receptors-bearing tumors are correlated with the mortality rate of the majority of breast cancer patients. Approximately 192,000 women would be diagnosed with breast cancer in the United States in 2009 with 40,000 resulting deaths.[1] Due to improved diagnostic and treatment strategies decreased the breast cancer mortality by 25% over the past 2 decades. Even though the mortality of cancer has decreased, the physical and psychological burdens of surgery, radiotherapy, hormonal and chemotherapy are substantial. For this reason, breast cancer prevention implies a major focus of current research, and it requires the basic understanding of molecular mechanisms of carcinogenesis.[2] The US medical organizations recommend screening mammography for women aged 40 years and older. The reason is it will reduce breast cancer mortality by about 20-35% in women aged 50–69 years and slightly less in women aged 40–49 years at 14 years of follow-up.[3] Estrogens are natural hormones important for early development of primary and secondary sexual characteristics, embryonal and fetal development of the brain networks.[4] They act through two types of their receptors: Classical nuclear receptors (ER-α and ER-β) and novel cell surface membrane receptors (GPR30 and ER-X before menopause), they are produced mainly in the ovaries. After menopause, they are produced mainly in fat tissue.

A common thread linking the main causes for developing breast cancer in women are due to the excessive exposure to estrogen. It causes increased cell proliferation through estrogen receptor (ER)-mediated signal transduction accompanied by increased probability for mutation to occur during DNA synthesis. This article provides a review on the estrogens and ER in the development of breast carcinogenesis and provides a paradigm for how estrogens may contribute to the development of human breast cancer. Some of the studies proved that the catechols themselves are signaling molecules that

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work through the ER.[5] Estrogens become endogenous carcinogen through the formation of catechol estrogen quinones, which react with DNA to form specific depurinating estrogen-DNA adducts. These mutations can lead to cell transformation initiation of breast cancer.[6]

ER IN BREAST CANCER

In females, ovary produces sex steroid hormone, estrogen and it affects growth, differentiation, and function of the mammary gland.[7] Three major forms of physiological estrogens are estrone (E1), estradiol (E2), and estriol (E3). The major estrogen hormone is estradiol (E2) which is an important role in the progression of breast cancer, and a majority of the human breast cancers was mostly estrogen dependent and express the ER. The biological effects of estrogen are mediated by binding to the structurally and functionally distinct ERs such as ER-α and ER-β.[8] The first receptor subtype identified in the breast was found to be ER-α, and so many studies have been focused on the biological role of ER-α in the mammary gland. However, recently, it has been shown that ER-β is also expressed in breast cancer, but its function remains unclear.[9] The expression of receptor ER-α was directly correlated with expression of insulin-like growth factor (IGF) signaling system, including the type 1 IGF-receptor and insulin-receptor substrate-1.[10]

ER-α and ER-β are present in many cell types including the endothelium, epithelium, muscle, bone, cartilage, hematopoietic cells, neurons, and glia [Table 1], and they exhibit a distinct pattern of tissue-specific distribution throughout the body. ER-α and ER-β are encoded by separate genes such as *ESR1* and *ESR2*, respectively, located on different chromosomes.[11]

The drugs such as antiestrogens (AEs) and aromatase inhibitors were used clinically to arrest the estrogen-dependent growth of breast cancer. Through the nuclear ERs, cytoplasmic or membrane ERs and G-protein-coupled ERs, estrogen produces its effects. These estrogen-binding systems bind with associating proteins to mediate the cell cycle signaling, proliferation, and survival. The newly identified proteins of nuclear ER are LKB1, PELP1, PAX-2, and FOXA1, whereas partners of extranuclear ER-α are PI3K and the tyrosine kinase Src. Breast cancer proliferation is enhanced by insulin and EGF, which targets the signaling pathways through the mitogen-activating protein kinase (MAPK) and PI3K/AKT pathways.[12]

Recently, it has been showed that hyperactivation of MAPK leads to downregulation of ER-α expression in breast cancer cells that overexpress epidermal growth factor receptor (EGFR).[13] Estrogen rapidly activates the MAPK such as Erk-1 and Erk-2, and it requires the expression of the G-protein-coupled receptor homolog, GPR30. MCF-7 cells which express both ER-α and ER-β get activated by estradiol which activates Erk-1/-2, and it also expressed in SKBR3 breast cancer cells, which fail to express either receptor. The estrogen response was associated with GPR30 protein, and it was analyzed by immunoblot analysis technique.[14]

REGULATION OF BIOMARKERS BY ESTROGEN IN BREAST CANCER

Estrogen plays an important role in breast cancer pathogenesis, and the estrogen/ER-mediated signaling cascade is the most effective means of treating ER-positive breast cancer patients. Studies proved that

Table 1: Distribution of estrogen receptors (ERs) in various tissues

ER subtypes	Distribution in peripheral tissues	Distribution in the brain
ER-α	Uterus, epididymis, bone, breast, liver, kidney, white adipose tissue, stroma of prostate, theca and interstitial cells of ovary, and Leydig cells of testes	Intensely in amygdala; bed nucleus of the stria terminals; periaqueductal gray; preoptic area. Moderately in allocortex; hypothalamus; locus coeruleus; spinal trigeminal nucleus
ER-β	Colon, testis, bone marrow, vascular endothelium, lung, bladder, epithelium of prostate, granulosa cells of ovary	Intensely in amygdala; bed nucleus of the stria terminals; raphe nuclei; substantial nigra. Moderately in allocortex; globus pallidus; hippocampus; locus coeruleus; preoptic area; ventral tegmental area
GPR30	Detected in adrenal medulla, renal pelvis, and ovary	Intensely in allocortex; anterior tegmental nucleus; cerebellum; hippocampus; hypothalamus; isocortex; locus coeruleus; pontine nuclei; preoptic area; spinal trigeminal nucleus; superior olive nucleus. Moderately in periaqueductal gray
ER-X	Enriched in the uterus and lung of the postnatal rodent; almost undetectable in the normal adult	Enriched in the fetal baboon brain and the neocortex of the postnatal rodent; almost undetectable in the normal adult

the regulation of HOXB13, IL17BR, and CHDH is mediated through the ER. These biomarkers were initially discovered as prognostic biomarkers in ER-positive patients treated with tamoxifen monotherapy,[15] and recently, studies undertaken to determine whether the estrogen response of these genes could be modulated by tamoxifen, a partial AE. HOXB13, IL17BR, and CHDH are estrogen-regulated genes, and their prognostic utility is likely to impact on their regulation through both ER- and HER2-dependent pathways.[16] PGRMC1 (progesterone receptor membrane component-1), a hormone receptor component, is a new biomarker for the ER in breast cancer. This biomarker either activates AKT by activating P450 proteins or directly binds to AKT activator.[17]

ER AND VARIOUS SIGNALLING PATHWAYS

Nearly 70% of breast cancers shows the expression of ER-α and is a key nuclear protein in ER-positive breast tumors. When it is activated by estrogens, ER acts as a ligand-dependent transcription factor, and it promotes the expression of several genes that enhance cell survival, proliferation, and tumor progression [Figure 1].[18,19] Estradiol is known to rapidly activate many signaling molecules such as IGF-IR, EGFR, and MAPK in breast cancer cells.

The estrogen action can be divided into two categories: (a) Classical receptor-mediated responses, utilizing membrane-bound ERs and (b) non-classical, non-receptor-mediated responses, mediated by GPR30 and ER-α3.[20,21] Genomic and extranuclear signaling pathways are the main two estrogen signaling pathway. In the genomic pathway, estradiol (E2) binds to ER-α and relocalizes estrogen to estrogen-responsive elements and promotes target genes expression. In the extranuclear signaling pathways, rapid E2 signaling activates PI3K/Akt/mTOR and eRK/MAPK pathway. Thus, estrogen signal regulates cell proliferation, apoptosis, and cell cycle, following control cell or tissue growth.

The biological actions of estradiol are regulated both by genomic effects (transcriptional effects inside the nucleus) and non-genomic effects (ER-α acting outside of the nuclear compartment). The non-genomic effects of estradiol (E2) lead to the rapid activation of many signaling molecules such as IGF-IR and EGFR, $p21^{ras}$ and Raf-1, MAPK and Akt, protein kinase C, release of nitric oxide and stimulation of prolactin secretion and alteration of calcium and Maxi-K channels. Both IGF-IR and EGFR initiate downstream signaling pathways such as activation of MAPK and Akt cascades.[22]

The gene products upregulated by ER actions are Bcl-2, cyclin D1, and the IGF-1 receptor.[23,24] Thus, the activated ER along with numerous different signaling molecules exerts rapid, non-genomic effects that lead to activation of growth and survival-promoting pathways including the MAPK and Akt pathways.[25]

CONCLUSION

On the basis of literature exploited in this review, it has been implemented that estrogen especially

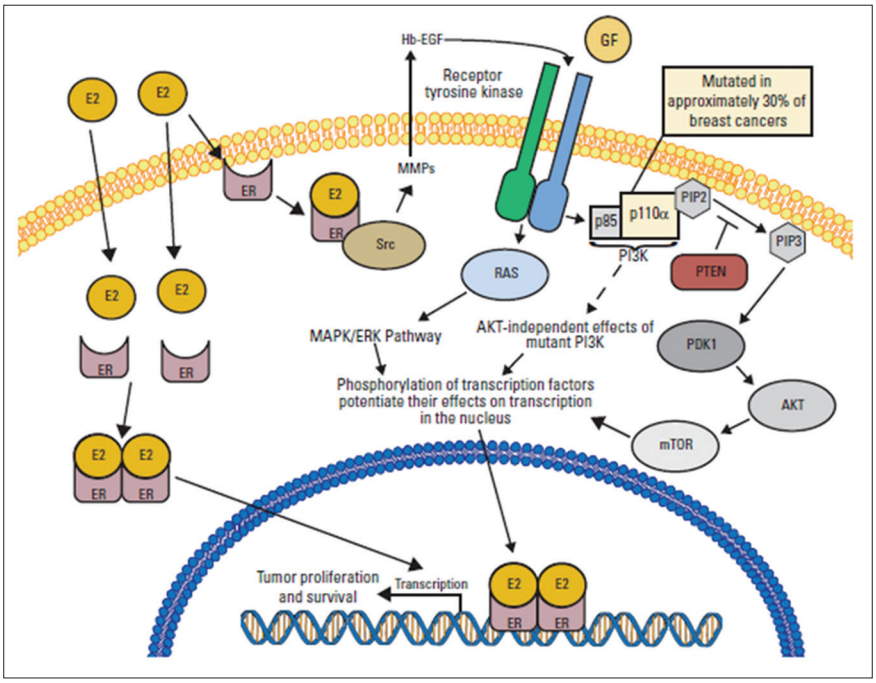

Figure 1: Estrogen action through estrogen receptor α and growth factor signaling pathways

estradiol (E2) is mainly involved in the breast cancer progression. Recent mechanistic studies highlighted the signaling pathways of ER-α toward the breast cancer. This signaling pathway provides new target for therapeutic intervention. Along with signaling pathway, it also established the various biomarkers or associated protein targets for breast cancer. Finally, we believe that estrogen is not only local sex hormones; it is an important target to develop the drugs, i.e., anti-estrogenic drugs for breast cancer.

REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics. CA Cancer J Clin 2009;59:225-49.
2. Yue W, Wang JP, Li Y, Fan P, Liu G, Zhang N, *et al*. Effects of estrogen on breast cancer development: Role of estrogen receptor independent mechanisms. Int J Cancer 2010;127:1748-57.
3. Elmore JG, Armstrong K, Lehman CD, Fletcher SW. Screening for breast cancer. JAMA 2005;293:1245-56.
4. Rao ML, Kölsch H. Effects of estrogen on brain development and neuroprotection–implications for negative symptoms in schizophrenia. Psychoneuroendocrinology 2003;28 Suppl 2:83-96.
5. Yager JD. Endogenous estrogens as carcinogens through metabolic activation. J Natl Cancer Inst Monogr 2000;27:67-73.
6. Gaikwad NW, Yang L, Muti P, Meza JL, Pruthi S, Ingle JN, *et al*. The molecular etiology of breast cancer: Evidence from biomarkers of risk. Int J Cancer 2008;122:1949-57.
7. Gross JM, Yee D. How does the estrogen receptor work. Breast Cancer Res 2002;4:62.
8. Thomas C, Gustafsson JA. The different roles of ER subtypes in cancer biology and therapy. Nat Rev Cancer 2011;11:597-608.
9. Roger P, Sahla ME, Mäkelä S, Gustafsson JA, Baldet P, Rochefort H, *et al*. Decreased expression of estrogen receptor beta protein in proliferative preinvasive mammary tumors. Cancer Res 2001;61:2537-41.
10. Oesterreich S, Zhang P, Guler RL, Sun X, Curran EM, Welshons WV, *et al*. Re-expression of estrogen receptor alpha in estrogen receptor alpha-negative MCF-7 cells restores both estrogen and insulin-like growth factor-mediated signaling and growth. Cancer Res 2001;61:5771-7.
11. Cui J, Shen Y, Li R. Estrogen synthesis and signaling pathways during aging: From periphery to brain. Trends Mol Med 2013;19:197-209.
12. Renoir JM, Marsaud V, Lazennec G. Estrogen receptor signaling as a target for novel breast cancer therapeutics. Biochem Pharmacol 2013;85:449-65.
13. Oh AS, Lorant LA, Holloway JN, Miller DL, Kern FG, El-Ashry D, *et al*. Hyperactivation of MAPK induces loss of ERalpha expression in breast cancer cells. Mol Endocrinol 2001;15:1344-59.
14. Filardo EJ, Quinn JA, Bland KI, Frackelton AR Jr. Estrogen-induced activation of erk-1 and erk-2 requires the G protein-coupled receptor homolog, GPR30, and occurs via trans-activation of the epidermal growth factor receptor through release of HB-EGF. Mol Endocrinol 2000;14:1649-60.
15. Ma XJ, Wang Z, Ryan PD, Isakoff SJ, Barmettler A, Fuller A, *et al*. A two-gene expression ratio predicts clinical outcome in breast cancer patients treated with tamoxifen. Cancer Cell 2004;5:607-16.
16. Wang Z, Dahiya S, Provencher H, Muir B, Carney E, Coser K, *et al*. The prognostic biomarkers HOXB13, IL17BR, and CHDH are regulated by estrogen in breast cancer. Clin Cancer Res 2007;13:6327-34.
17. Craven RJ. PGRMC1: A new biomarker for the estrogen receptor in breast cancer. Breast Cancer Res 2008;10:113.
18. Osborne CK, Schiff R. Estrogen-receptor biology: Continuing progress and therapeutic implications. J Clin Oncol 2005;23:1616-22.
19. Shao W, Brown M: Advances in estrogen receptor biology: Prospects for improvements in targeted breast cancer therapy. Breast Cancer Res 2004;6:39-52.
20. Prossnitz ER, Arterburn JB, Smith HO, Oprea TI, Sklar LA, Hathaway HJ, *et al*. Estrogen signaling through the transmembrane G protein-coupled receptor GPR30. Annu Rev Physiol 2008;70:165-90.
21. Kang L, Zhang X, Xie Y, Tu Y, Wang D, Liu Z, *et al*. Involvement of estrogen receptor variant ER-alpha36, not GPR30, in nongenomic estrogen signaling. Mol Endocrinol 2010;24:709-21.
22. Skandalis SS, Afratis N, Smirlaki G, Nikitovic D, Theocharis AD, Tzanakakis GN, *et al*. Cross-talk between estradiol receptor and EGFR/IGF-IR signaling pathways in estrogen-responsive breast cancers: Focus on the role and impact of proteoglycans. Matrix Biol 2014;35:182-93.
23. Arpino G, Wiechmann L, Osborne CK, Schiff R. Crosstalk between the estrogen receptor and the HER tyrosine kinase receptor family: Molecular mechanism and clinical implications for endocrine therapy resistance. Endocr Rev 2008;29:217-33.
24. Klinge CM, Jernigan SC, Smith SL, Tyulmenkov VV, Kulakosky PC. Estrogen response element sequence impacts the conformation and transcriptional activity of estrogen receptor alpha. Mol Cell Endocrinol 2001;174:151-66.
25. Song RX. Membrane-initiated steroid signaling action of estrogen and breast cancer. Semin Reprod Med 2007;25:187-97.

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