MINI-REVIEW

Estrogen Receptor α Roles in Breast Cancer Chemoresistance

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Abstract

Resistance to chemotherapy treatment, which may lead to limited efficacy of systemic therapy in breast cancer patients, is multifactorial. Among the mechanisms of resistance to chemotherapy treatment, there are those closely related to estrogen receptor α, P-glycoprotein, multidrug resistance-related protein, glutathione S-transferase pi and topoisomerase-II. ERα is ligand-activated transcription factor that regulates gene expression and plays a critical role in endocrine signaling. In previous preclinical and clinical studies, positive ERα expression in breast cancer cells was correlated with decreased sensitivity to chemotherapy. This article reviews current knowledge on the predictive value of ERα with regard to response to chemotherapy. Better understanding of its role may facilitate patient selection of therapeutic regimens and lead to optimal clinical outcomes.

Keywords: Estrogen receptor α - chemoresistance - breast cancer - Fulvestrant

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Introduction

The estrogen receptor α (ERα) plays an important role in the progression of breast cancer. About 65% of the human breast cancers were estrogen dependent and express ER α (Puhalla et al., 2012; Xu et al., 2012). Chemotherapy is a critically important treatment choice for most breast cancer patients, which has been shown to substantially improve disease-free survival and overall survival, but chemotherapy often fails to cure the disease due to unexpected drug resistance (Karroum et al., 2012; Natarajan et al., 2012). In recent years, accumulative data from clinical trials and laboratory trials suggested that ERα status might also affect the efficacy of chemotherapy. Specifically, it has been observed that some chemotherapeutic agents may be less effective in patients with ERα+ tumors than those with ERα- tumors (Precht et al., 2010; Bailey et al., 2012; Lips et al., 2012). These findings indicate that ERα status may play an important role in determining the sensitivity of breast tumors to chemotherapy.

Drug resistance is one of the major obstacles limiting the success of breast cancer chemotherapy. In this field, inherent or acquired chemotherapy resistance, which can include development of resistance to multiple drugs, is a frequent phenomenon in breast cancer cells. Forty percent of breast cancer patients with surgery and 80% of breast cancer patients with unresectable disease have poor response to chemotherapy (Petit et al., 2010; Osako et al., 2012). Several mechanisms of drug resistance have been examined. Overexpression of a membrane efflux transporter, P-glycoprotein (P-gp) (Shi et al., 2011), overexpression of multidrug resistance (MDR)-associated protein (Romero et al., 2011), changes in topoisomerase II activity (Romero et al., 2011), modifications in glutathione S-transferase (Romero et al., 2012), and altered expression of apoptosis-associated protein Bcl-2 (Bjerre et al., 2012; Larsen et al., 2012) and tumor suppressor protein p53 (Bailey et al., 2012). ERα status, although lesser known, have also been studied in connection with MDR.

Estrogen receptor and its isoforms

Estrogen receptors are ligand-regulated transcription factors; its biological action is mediated by binding to estrogen. Ligand-binding induces conformation changes in the receptor leading to dimerization, protein-DNA interaction, recruitment of co-regulator proteins and other transcription factors and ultimately the formation of the pre-initiation complex. The Estrogen receptors including isoforms ERα and ERβ, both receptors are expressed in breast cancer. ERα and ERβ have a common structural architecture composed of three functional domains including the N-terminal A/B domain, the C or DNA-binding domain and the D/E/F or ligand-binding domain. ERα isoform has attracted a great deal of attention as a key molecule in the progression of breast cancer.

The ERα consists of at least three different variants. ERα66, which was a full-length counterpart divided into six distinct regions (A-F), was the first identified estrogen receptor (Figure 1). The N-terminal domain A/B is the ligand-independent transactivation function (AF-1). Domain C is the receptor dimerization and the binding to specific DNA sequences. The C-terminal domain E/F is

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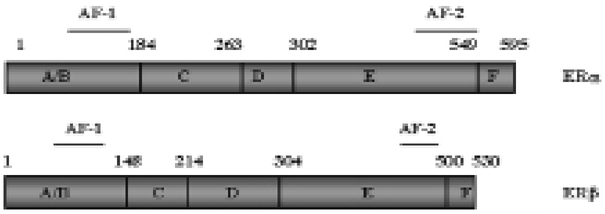

Figure 1. ERα and ERβ was a Full-length Counterpart Divided into Six Distinct Regions (A-F)

the ligand-dependent transactivation (AF-2). In contrast to its full-length counterpart, the truncated ERα46 lacks the transactivation domain AF-1 and encodes a protein with a predicted molecular weight of 46kDa. This ERα36 variant lacks both transactivation domains AF-1 and AF-2 compared to ERα66 and encodes a 36kDa protein.

Estrogen receptor α function

Estrogen receptor, ERα, for 17β-oestradiol, was first identified from rat uteri in 1966. Human ERα is located on human chromosome 6q25, first cloned in 1986. Estrogens are steroid hormones, which is associated with the human female reproductive cycle, interaction with estrogen receptors affect the growth, differentiation, and function of target tissues. Binding of ERα causes a conformational change allowing disassociation from co-repressors and recruitment of co-activator molecules. Estrogen-bound ERα translocation to the nucleus, where they increased transcription of target genes by two different mechanisms, classical pathway where ERα binds to estrogen-response element (ERE) and modulates target genes (Figure 2) and non-classical pathway where ERα binds to co-activator molecules, such as specificity protein 1 (Sp1), activating protein 1 (AP-1), or nuclear factor kappa b (NF-kB), associated with their recognition sites in enhancer elements and modifies their function.

Significance of ERα in breast cancer diseases

The attempt to define the prognostic and treatment value of ERα expression concerning mainly breast cancer patients treated has already been undertaken by many researchers.

The breast cancer patients with high ERα expression were benefit from endocrine therapy (selective estrogenreceptor modulators or aromatase inhibitors) (Kemp et al., 2011; Geisler et al., 2012; Goncalves et al., 2012; Walker et al., 2012; Walker et al., 2012). Tamoxifen (selective estrogenreceptor modulators) is currently used in both premenopausal and postmenopausal breast cancer patients with ERα positive expression (Fisher et al., 1996; Fleeman et al., 2011). The Early Breast Cancer Trialists Collaborative Group meta-analysis of 194 randomized trials employing adjuvant chemotherapy and endocrine therapy demonstrated the 15-year breast cancer recurrence rate was reduced from 45% to 33% with use of tamoxifen, and reduction of breast cancer mortality by 35% (EBCTCG et al., 2008). This meta-analysis determined that the risk of the breast cancer patients with ERα positive expression was reduction with tamoxifen both in premenopausal and postmenopausal women.

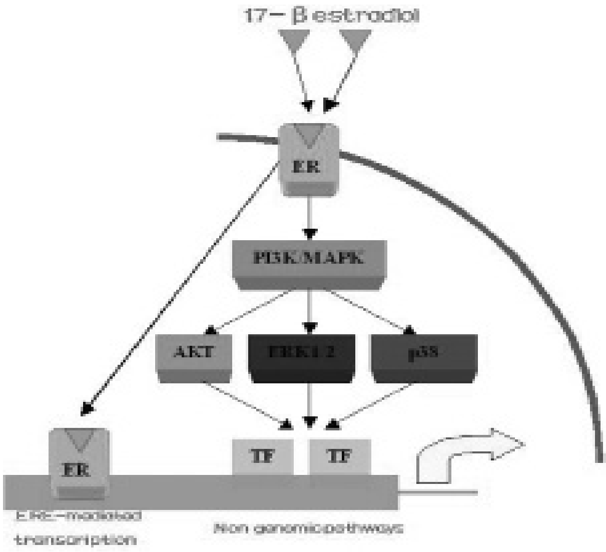

Figure 2. Mechanisms of ERα Signaling: Convergence of Genomic and Nongenomic Actions on Target Genes

Tamoxifen has shown benefit to women with ERα positive expression breast cancers irrespective of menopausal status. However, a number of studies evaluating the use of aromatase inhibitors as an alternative to tamoxifen in postmenopausal women with ERα positive expression breast cancers, in the past 10 years (Bachelot et al., 2012; Gilani et al., 2012). In contrast to tamoxifen, aromatase inhibitors act by preventing the conversion of androgens to estrogens by blocking the aromatase enzyme and result in subsequent decline in estrogens levels (Saylam et al., 2011). In postmenopausal women aromatase inhibitors agents offer the advantage of modestly improved activity over tamoxifen, and aromatase inhibitors agents do not possess the thrombotic or endometrial cancer risks (Cohen et al., 2008; Coleman et al., 2008).

Resistance to chemotherapy in ERα positive breast cancer

The potential association between expression of ERα in breast tumors and resistance to chemotherapy treatment was first reported about two decades age (Tokuda et al., 2012). In a retrospective study, thirty-four of 45 patients with low or absent ERα expression level had objective responses to chemotherapy, whereas only three of 25 patients with higher ERα expression responses to chemotherapy. Since then, many papers have indicated that expression level of ERα may interfere with the therapeutic efficacy of chemotherapy in breast tumors (Dziadyk et al., 2004; Mutoh et al., 2006; Tabuchi et al., 2009). To identification the role of ERα in breast cancer threatment, the 97 breast cancer patients were studied, including the expression level of Bcl-2, ERα, P53 HER2 and Ki-67 associated with neoadjuvant chemotherapy response. The results showed that ERα negativity is associated with better chemotherapy response (Wang et al., 2009). The similar results were showed in others (Lv et al., 2011; Jeong et al., 2012).

The neoadjuvant chemotherapy permits the assessment of pathologic response of the primary cancer tissues to chemotherapy treatment and provides an early opportunity to alter the agents if the cancer tissues appear chemotherapy resistant. In recently our retrospective study, 118 primary breast tumor patients with neoadjuvant chemotherapy were investigated (Wang et al., 2009). The result showed that ERα is an independent predictive factor for pathologic response to neoadjuvant chemotherapy in primary breast tumors. Another study showed the similar results, preoperational biopsies from 517 patients with locally advanced breast cancer were analyzed for expression of ERα, and these data were compared to the pathological response after preoperative chemotherapy (+/- radiotherapy). The result showed that patients with locally advanced breast cancer, lower ERα had a significantly greater benefit from chemotherapy.

In laboratory study showed that the combination of paclitaxel with exemestane, a non-steroidal aromatase inhibitor that shuts down estrogen synthesis, produced additive antitumor effect in human breast cancer cell lines (Chen et al., 2004). Another study conducted by Wu et al. showed that arzoxifene, a short-acting selective estrogen receptor modulator (SERMs), can inhibit repopulation of ERα MCF-7 breast cancer xenograft tumors when given between courses of chemotherapy (5-fluorouracil or paclitaxel) (Wu et al., 2005). These findings suggest that the combined use of endocrine therapy agents with chemotherapeutic drug might benefit the clinical treatment for ERα breast cancer patients.

ERα may play an important role in determining the sensitivity of breast tumors to chemotherapy treatment, but the mechanisms ERα–mediated drug resistance is not entirely clear. In a recently study, sui et al. stable transfection and expression of ERα result in reduced sensitivity of BCap37 cells to paclitaxel, particularly to paclitaxel-induced apoptotic cell death. The potential mechanisms indicate that several apoptosis associated proteins, including bcl-2 and IκB exhibit differential responses to paclitaxel in BCap37 cells with ER positive expression (Sui et al., 2007). However, there are different opinions in this study. The ERαtransfected Bcap37 cells and natural ERαpositive T47D breast cancer cells were treated using chemotherapeutic agents with or without 17-beta estradiol (E2) pretreatment. The breast cancer cells with ERα positive were decreased in response to chemotherapeutic agents due to the influence of ERαon the growth of breast cancer cells (Jiang et al., 2012). It is important to note that the exact molecular mechanisms by which ERαresistance to chemotherapy treatment remain unclear, even though the known ERαis well documented for their oncogenic roles in cancer development and progression.

ICI 182,780 sensitizes ERα positive breast cancer cells to chemotherapy treatment

The next obvious question is the if down-regulates the expression of ERαin breast cancer cells could sensitizes cancer cells to the treatment of chemotherapy. ICI 182,780(Fulvestrant) is a potent steroidal antiestrogen, which can bind to both estrogen receptor subtypes, as well as for estradiol, are distinct on both ERαand ERβ. ICI 182,780 caused a gradual but dramatic decrease in ERαexpression in the human tissues, but no change ERβexpression (Oliveira et al., 2003) ICI 182,780, a steroidal pure antiestrogen agent, dramatically down-regulates ERα protein levels.

In this regard, several studies have shed light on the ICI 182,780 sensitizes ERα breast cancer cells to chemotherapy treatment. For instance, Sui et al. demonstrated that ICI 182,780 could significantly sensitized ERα breast cancer cells cells to chemotherapy drug-induced G2/M arrest and changes in IκBa and bcl-2 (Sui et al., 2007). Moreover, ICI 182,780 was also reported to changes in Bax and bcl-2 in ERα breast cancer cells. It is thus possible that ICI 182,780 could reduce the expression of ERα in breast cancer cell, which can sensitize ERα breast cancer cells to chemotherapy treatment.

Summary

The past several years have seen significant strides in elucidating the role of ERα in breast cancer drug resistance. It is clear that ERα exerts a negative effect on cancer treatment outcomes by virtue of its effects on anticancer drug.

Data are starting to accumulate defining the role that ERα play in the chemotherapy treatment. Although some studies found enhanced drug toxicity or more favorable tumor response with ICI 182,780 treatment in breast cancer cells with ERα expression, other studies did not substantiate these findings. Further work in this area is clearly needed.

Given this, in the foreseeable future, drug treatment may be guided by individualized genotype databases that can enable customized drug dosing to minimize toxicity and to enhance therapeutic effect. The past several years have provided mounting evidence for expression of ERα in breast cancer and ERα expression frequently correlates with chemotherapy-resistant disease.

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References

Bachelot T, Bourgier C, Cropet C, Ray-Coquard I, et al (2012). Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors, a GINECO study. *J Clin Oncol*, **30**, 2718-24.

Bailey ST, Shin H, Westerling T, et al (2012). Estrogen receptor prevents p53-dependent apoptosis in breast cancer. *Proc Natl Acad Sci U S A*, **109**, 18060-5.

Bailey ST, Shin H, Westerling T, et al (2012). Estrogen receptor prevents p53-dependent apoptosis in breast cancer. *Proc Natl Acad Sci U S A*, **109**, 18060-5.

Chen D, Hackl W, Ortmann O, et al (2004). Effects of a combination of exemestane and paclitaxel on human tumor cells in vitro. *Anticancer Drugs*, **15**, 55-61.

Cohen I (2008). Aromatase inhibitors and the endometrium. *Maturitas*, **59**, 285-92.

Coleman RE, Body JJ, Gralow JR, et al (2008). Bone loss in patients with breast cancer receiving aromatase inhibitors and associated treatment strategies. *Cancer Treat Rev*, **34**, S31-42.

Dönmez Y, Akhmetova L, İşeri ÖD, Kars MD, Gündüz U (2011). Effect of MDR modulators verapamil and promethazine on gene expression levels of MDR1 and MRP1 in doxorubicin-resistant MCF-7 cells. *Cancer Chemother Pharmacol*, **67**, 823-8.

Dziadyk JM, Sui M, Zhu X (2004). Paclitaxel-induced apoptosis may occur without a prior G2/M-phase arrest. *Anticancer Res*, **24**, 27-36.

Early Breast Cancer Trialists Collaborative Group (EBCTCG), Clarke M, Coates AS, et al (2008). Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer, patient-level meta-analysis of randomised trials. *Lancet*, **371**, 29-40.

Fisher B, Dignam J, Bryant J, et al (1996). Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. *J Natl Cancer Inst*, **88**, 1529-42.

Fleeman N, Martin Saborido C, Payne K, et al (2011). The clinical effectiveness and cost-effectiveness of genotyping for CYP2D6 for the management of women with breast cancer treated with tamoxifen, a systematic review. *Health Technol Assess*, **15**, 1-102.

Geisler J, Smith I, Miller W (2012). Presurgical (neoadjuvant) endocrine therapy is a useful model to predict response and outcome to endocrine treatment in breast cancer patients. *J Steroid Biochem Mol Biol*, **131**, 93-100.

Gilani RA, Kazi AA, Shah P, et al (2012). The importance of HER2 signaling in the tumor-initiating cell population in aromatase inhibitor-resistant breast cancer. *Breast Cancer Res Treat*, **135**, 681-92.

Goncalves R, Ma C, Luo J, et al (2012). Use of neoadjuvant data to design adjuvant endocrine therapy trials for breast cancer. *Nat Rev Clin Oncol*, **9**, 223-9.

Jeong JH, Jung SY, Park IH, et al (2012). Predictive factors of pathologic complete response and clinical tumor progression after preoperative chemotherapy in patients with stage II and III breast cancer. *Invest New Drugs*, **30**, 408-16.

Jiang Z, Guo J, Shen J, et al (2012). The role of estrogen receptor alpha in mediating chemoresistance in breast cancer cells. *J Exp Clin Cancer Res*, **31**, 42.

Karroum A, Mirshahi P, Faussat AM, et al (2012). Tubular network formation by adriamycin-resistant MCF-7 breast cancer cells is closely linked to MMP-9 and VEGFR-2/VEGFR-3 over-expressions. *Eur J Pharmacol*, **685**, 1-7.

Kemp Z, Jones A (2011). A shift in the treatment of hormone receptor and human epidermal growth factor receptor 2-positive metastatic breast cancer. *Adv Ther*, **28**, 603-14.

Larsen MS, Bjerre K, Giobbie-Hurder A, et al (2012). Prognostic value of Bcl-2 in two independent populations of estrogen receptor positive breast cancer patients treated with adjuvant endocrine therapy. *Acta Onco*, **51**, 781-9.

Lips EH, Mulder L, de Ronde JJ, et al (2012). Neoadjuvant chemotherapy in ER+ HER2- breast cancer, response prediction based on immunohistochemical and molecular characteristics. *Breast Cancer Res Treat*, **131**, 827-36.

Lv M, Li B, Li Y, et al (2011). Predictive role of molecular subtypes in response to neoadjuvant chemotherapy in breast cancer patients in Northeast China. *Asian Pac J Cancer Prev*, **12**, 2411-7.

Mutoh K, Tsukahara S, Mitsuhashi J, et al (2006). Estrogen-mediated post transcriptional down-regulation of P-glycoprotein in MDR1-transduced human breast cancer cells. *Cancer Sci*, **97**, 1198-204.

Natarajan K, Xie Y, Baer MR, et al (2012). Role of breast cancer resistance protein (BCRP/ABCG2) in cancer drug resistance. *Biochem Pharmacol*, **83**, 1084-103.

Oliveira CA, Nie R, Carnes K, et al (2003). The antiestrogen ICI 182,780 decreases the expression of estrogen receptor-alpha but has no effect on estrogen receptor-beta and androgen receptor in rat efferent ductules. *Reprod Biol Endocrinol*, **1**, 75.

Osako T, Nishimura R, Okumura Y, et al (2012). Predictive significance of the proportion of ER-positive or PgR-positive tumor cells in response to neoadjuvant chemotherapy for operable HER2-negative breast cancer. *Exp Ther Med*, **3**, 66-71.

Petit T, Wilt M, Velten M, et al (2010). Semi-quantitative evaluation of estrogen receptor expression is a strong predictive factor of pathological complete response after anthracycline-based neo-adjuvant chemotherapy in hormonal-sensitive breast cancer. *Breast Cancer Res Treat*, **124**, 387-91.

Precht LM, Lowe KA, Atwood M, et al (2010). Neoadjuvant chemotherapy of breast cancer, tumor markers as predictors of pathologic response, recurrence, and survival. *Breast J*, **16**, 362-8.

Puhalla S, Bhattacharya S, Davidson NE (2012). Hormonal therapy in breast cancer, a model disease for the personalization of cancer care. *Mol Oncol*, **6**, 222-36.

Romero A, Mart n M, Cheang MC, et al (2011). Assessment of Topoisomerase II α status in breast cancer by quantitative PCR, gene expression microarrays, immunohistochemistry, and fluorescence in situ hybridization. *Am J Pathol*, **178**, 1453-60.

Romero A, Mart n M, Oliva B, et al (2012). Glutathione S-transferase P1 c.313A > G polymorphism could be useful in the prediction of doxorubicin response in breast cancer patients. *Ann Oncol*, **23**, 1750-6.

Saylam B, Efesoy O, Cayan S (2011). The effect of aromatase inhibitor letrozole on body mass index, serum hormones, and sperm parameters in infertile men. *Fertil Steril*, **95**, 809-11.

Shi R, Li W, Zhang X, et al (2011). A novel indirubin derivative PHII-7 potentiates adriamycin cytotoxicity via inhibiting P-glycoprotein expression in human breast cancer MCF-7/ADR cells. *Eur J Pharmacol*, **669**, 38-44.

Sui M, Huang Y, Park BH, et al (2007). Estrogen receptor alpha mediates breast cancer cell resistance to paclitaxel through inhibition of apoptotic cell death. *Cancer Res*, **67**, 5337-44.

Tabuchi Y, Matsuoka J, Gunduz M, et al (2009). Resistance to paclitaxel therapy is related with Bcl-2 expression through an estrogen receptor mediated pathway in breast cancer. *Int J Oncol*, **34**, 313-9.

Tokuda E, Seino Y, Arakawa A, et al (2012). Estrogen receptor-_ directly regulates sensitivity to paclitaxel in neoadjuvant chemotherapy for breast cancer. *Breast Cancer Res Treat*, **133**, 427-36.

Walker CH, Drew BA, Antoon JW (2012). Neurocognitive effects of chemotherapy and endocrine therapies in the treatment of breast cancer, recent perspectives. *Cancer Invest*, **30**, 135-48.

Wang L, Jiang Z, Sui M, et al (2009). The potential biomarkers in predicting pathologic response of breast cancer to three different chemotherapy regimens, a case control study. *BMC Cancer,* **9**, 226.

Wu L and Tannock IF (2005). Effect of the selective estrogen receptor modulator arzoxifene on repopulation of hormone-responsive breast cancer xenografts between courses of chemotherapy. *Clin Cancer Res*, **11**, 8195-200.

Xu C, Li J, Lu Y, et al (2012). Estrogen receptor α and hedgehog signal pathway developmental biology of gastric adenocarcinoma. *Hepatogastroenterology*, **59**, 1319-22.