Unraveling the Mechanisms of Endocrine Resistance in Breast Cancer: New Therapeutic Opportunities

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Abstract Two thirds of breast cancers express the estrogen receptor (ER), which contributes to tumor development and progression. ER-targeted therapy is therefore widely used in breast cancer to inhibit signaling through ER and disrupt breast cancer growth. This therapeutic strategy, particularly using the antiestrogen tamoxifen, is proven to increase the cure rates in early breast cancer, improve patient outcomes in advanced disease, and reduce breast cancer incidence in the prevention setting. Despite the recent integration of more powerful endocrine agents into breast cancer care, resistance to all forms of endocrine therapy remains a major problem. New insight into ER biology and progress in understanding resistance mechanisms, mediated by molecular crosstalk between ER and various growth factor signaling pathways, are generating tremendous promise for new therapeutic opportunities to target resistance and improve breast cancer disease outcomes.

Background

Estrogen receptor (ER), which belongs to a larger family of nuclear receptors (1), is activated by estrogen binding, which leads to receptor phosphorylation, dimerization, and recruitment of coactivator proteins to the estrogen-bound receptor complex (2). This complex then binds promoter regions of target genes via direct interaction with DNA binding sites referred to as estrogen response elements (ERE) and initiates transcriptional activity. Estrogen-bound ER can also transactivate additional key target genes via protein-protein interaction with other transcription factors such as the Jun/Fos activator protein 1 (AP-1) transcription complex (3) and specificity protein 1 (SP-1; ref. 4), among others. Subsequent translation produces proteins that are instrumental in cell division, angiogenesis, and survival, leading to sustained breast cancer growth and progression (5). The antiestrogen tamoxifen, which has been the mainstay of endocrine therapy for the past 25 years, works by binding to ER in place of estrogen and altering the molecular conformation of the receptor (6). This leads to preferential recruitment of corepressor instead of coactivator proteins and, as a result, blocks the transcriptional activation functions of ER and subsequent tumor growth. The absolute and relative levels of these ER coactivator and corepressor proteins in a cancer cell may determine the agonist versus antagonist activities of tamoxifen and can therefore influence endocrine sensitivity. In addition, both experimental and clinical evidences suggest that phosphorylation of ER and its coregulators can also alter their interaction and may augment ER transcriptional activity in a ligand-independent mode or even in the presence of selective ER modulators (SERM) like tamoxifen (7).

In addition to the above-described classic or "genomic" ER action [also called nuclear initiated steroid signaling (NISS); ref. 8], a portion of the ER pool in a breast cancer cell may initiate more rapid cellular signaling by direct interaction with components of growth factor signaling pathways (9). This "nongenomic" ER action [also referred to as membrane-initiated steroid signaling (MISS); ref. 8] has been described in many target organs and tissues (10–12), including breast cancer cells (13, 14) and, importantly, can be activated by both estrogen and SERMs like tamoxifen. Activation of ER outside the nucleus leads to phosphorylation, and as a result, activation of surface tyrosine kinase receptors such as the insulin-like growth factor I receptor (IGF-IR; refs. 15, 16), the epidermal growth factor receptor (EGFR; ref. 17), and HER2 (18). ER can also associate with cellular kinase and adaptor molecules such as c-Src (19), Src homology and collagen homology protein (Shc; ref. 20), and the p85α regulatory subunit of phosphoinositide-3-kinase (21). Many of these interactions lead to the activation of key downstream signaling kinases such as the p42/44 mitogen-activated protein kinase (MAPK) and AKT, which orchestrate cell proliferation and survival. In addition, these signaling kinases can, in turn, phosphorylate and, therefore, activate ER itself or its coactivator proteins, which augments ER genomic signaling and promotes tamoxifen resistance. This bidirectional crosstalk between ER and growth factor receptor pathways helps sustain activation of pathway signaling and ensures the survival of a breast cancer cell even in the presence of tamoxifen (22).

Other forms of endocrine therapy have become available over the last decade, including the aromatase inhibitors (23), which block production of the estrogen ligand needed to activate ER, and the more potent ER antagonists such as fulvestrant, which degrade the ER protein itself (24). These

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agents can block the nongenomic as well as the genomic actions of ER and, therefore, may have a therapeutic advantage over SERMs like tamoxifen. In particular, aromatase inhibitors, which suppress tumor and plasma estrogen levels, are rapidly replacing tamoxifen as first-line therapy in various clinical settings. Despite these recent therapeutic developments, resistance to all forms of endocrine therapy still limits our ability to take full advantage of ER inhibition in breast cancer treatment. Recent advances in understanding the mechanisms of resistance to endocrine therapies promise to further refine our treatment approach, and potentially improve outcome of patients with ER-dependent breast cancer.

Clinical-Translational Advances

Implication of ER growth factor crosstalk in endocrine resistance and novel therapeutic approaches

Clinical evidence suggests that overexpression of growth factor receptors in breast cancer, especially those of the EGFR/HER2 family, is associated with resistance to endocrine therapy and, in particular, to tamoxifen (refs. 25–28; Fig. 1). Overexpression of these growth factor surface receptors further enhances crosstalk with the ER pathway and amplifies ER activation functions (22, 29), rendering a breast cancer cell resistant to endocrine therapy (30). Indeed, published evidence suggests that overexpression of growth factor receptors such as EGFR/HER2 augments both the genomic and nongenomic ER actions in breast cancer, leading, in turn, to tamoxifen resistance (18, 22, 31). Interestingly, whereas tamoxifen activates both genomic and nongenomic ER function when HER2 is overexpressed in MCF-7 cells *in vitro* (22), tumors formed by the same overexpressing cells *in vivo* are predominantly driven by nongenomic ER activation as the mechanism of *de novo* tamoxifen-stimulated growth (32). Subsequent studies show that these tamoxifen-resistant HER2-overexpressing breast tumors remain sensitive to estrogen deprivation and to the pure ER antagonist fulvestrant (33), indicating their continued dependence on ER for growth. Removing the estrogen ligand or down-regulation of the ER itself in this instance may offer a more complete blockade of nongenomic as well as genomic ER activities and, thus, may lessen the crosstalk that leads to resistance (Fig. 1). Clinical trials in the neoadjuvant setting, which allow direct observation of response to treatment, confirm that whereas breast cancers with elevated EGFR/HER2 expression exhibit increased intrinsic tamoxifen resistance, they remain sensitive to estrogen deprivation by aromatase inhibitors (34–36), thus confirming preclinical observations on the relationship between HER2 overexpression and endocrine response. Sensitivity to estrogen deprivation and fulvestrant in these HER2-overexpressing tumors, however, is short lived, as was shown both in preclinical (33) and in clinical studies with aromatase inhibitor therapy (37), most probably due to the overactivation of EGFR/HER2 signaling. Consequently, it may be prudent to simultaneously target growth factor receptor signaling in addition to ER itself to optimize therapeutic benefit. Indeed, xenograft studies confirm that targeting HER2 signaling in combination with endocrine therapy in HER2-overexpressing xenografts restores tamoxifen sensitivity and significantly delays resistance to estrogen

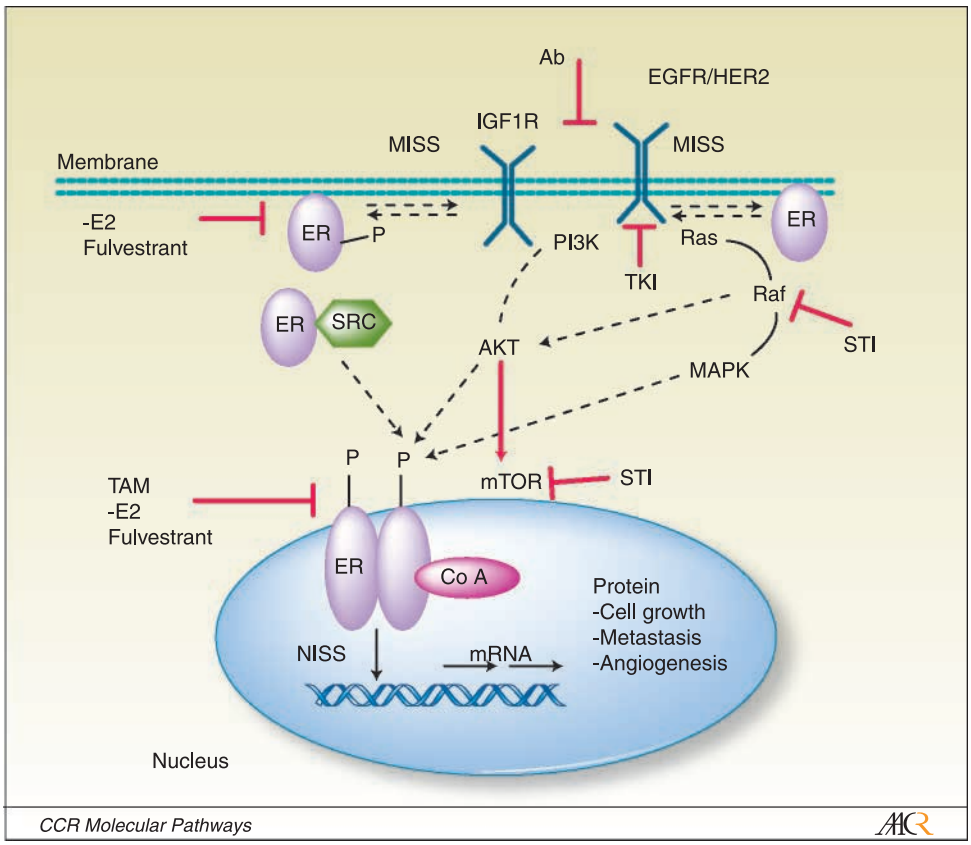

Fig. 1. ER crosstalk with growth factor receptor pathways in breast cancer—a working model of endocrine resistance. In most ER-positive tumors, genomic ER activity in which ER acts as a transcription factor in the nucleus (also known as NISS) predominates, although some nongenomic ER activity, mediated by ER in the plasma membrane or the cytoplasm interacting with various growth factor receptor and cellular kinase signaling molecules (also known as MISS) also occurs. In tumors with overexpression or hyperactivation of EGFR/HER2, however, ER MISS activity may be especially enhanced. Both genomic/NISS and nongenomic/MISS ER activities are augmented in these tumors via molecular crosstalk between the coexpressed pathways. SERMs like tamoxifen usually inhibit NISS but have no effect or may even promote nongenomic/MISS ER activity. In contrast, estrogen deprivation (−E2) using aromatase inhibitors, or pure antiestrogens such as fulvestrant, can block both NISS and MISS ER activities and, thus, halt the crosstalk with growth factor receptor pathways. Targeting the growth factor receptor pathway at different nodal points of signaling using tyrosine kinase inhibitors (TKI), antibodies (Ab), or other signal transduction inhibitors (STI, e.g., mTOR and Raf inhibitors), can eliminate the molecular crosstalk and overcome endocrine resistance.

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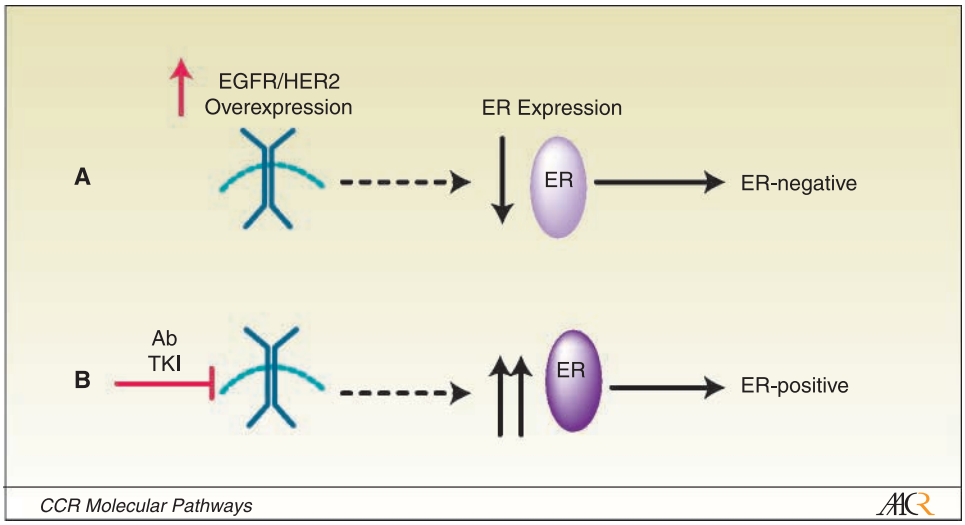

Fig. 2. Interplay between growth factor receptors and ER expression. *A,* overactivation of EGFR/HER2 or its downstream signaling elements, such as p42/44 MAPK, down-regulates or completely represses the ER, resulting in apparently ER-negative tumors that do not respond to endocrine therapy. *B,* inhibition of this hyperactive EGFR/HER2 signaling by tyrosine kinase inhibitors (TKI), antibodies (Ab), or other signal transduction inhibitors, can restore ER expression in these apparently ER-negative tumors, and thus, may reestablish endocrine sensitivity.

deprivation and fulvestrant (22, 33). This data has significant potential implications for patient care, and ongoing clinical trials are examining the combination of EGFR/HER2 blocking agents such as trastuzumab, and the tyrosine kinase inhibitors gefitinib and lapatinib, together with endocrine therapy in ER-positive tumors that coexpress these HER receptors.

EGFR/HER2 levels can also become elevated in tumors with low growth factor receptor expression that are initially endocrine sensitive but later develop acquired resistance. Tamoxifen-treated MCF-7 tumor cells show increased dependence on EGFR as they become resistant, both *in vitro* (38) and *in vivo* (39). Similarly, fulvestrant-treated MCF-7 cells have elevated EGFR levels, suggesting a role in acquired resistance to fulvestrant as well (40). In both instances, inhibition of EGFR signaling can overcome resistance to tamoxifen and fulvestrant and delay the emergence of therapeutic resistance. Interestingly, activation of certain downstream signaling molecules such as p42/44 MAPK (41) and AKT (42–44) may also be associated with endocrine resistance, so that targeting these signaling elements or their downstream effectors (45, 46) may modulate endocrine response and delay resistance.

Ongoing clinical studies are examining whether combining endocrine therapy with a variety of novel targeted therapies may help overcome endocrine resistance and improve treatment outcomes. With the increasing availability of agents that target cancer growth at different signaling levels, clinical trials are looking at combinations of endocrine therapies with a variety of monoclonal antibodies, tyrosine kinase inhibitors, Raf kinase inhibitors, farnesyl transferase inhibitors, and mTOR inhibitors, among others (47). Interestingly, more recent experimental evidence also suggests that to more effectively overcome endocrine resistance, a more complete blockade of growth factor receptor pathways may be needed (48). Thus, either multiple signaling inhibitors or agents with multiple kinase targeting capabilities may need to be tested together with endocrine therapy. Careful selection of patients, however, will be important in determining the outcomes of planned trials, and biopsy studies during therapy will help validate molecular targets in parallel with clinical end points.

Dynamic interplay of ER and growth factor receptor expression: more therapeutic opportunities

In addition to molecular crosstalk between ER and coexpressed growth factor receptor pathways, there is evidence supporting a dynamic inverse relationship between expression of growth factor receptors and ER (Fig. 2). Indeed, it has been known for some time that breast cancers with HER2 overexpression are more likely to be ER negative, and that ER content is inversely correlated with EGFR/HER2 levels in tumors that express both receptors (49, 50). Preclinical data suggest that increased growth factor signaling induced by receptor-specific ligands like EGF, IGF-1, transforming growth factor-β, and heregulin can down-regulate ER protein expression and lead to a more endocrine-independent phenotype (51–53). In other experiments, transfection of constitutively active growth factor receptors or signaling molecules such as activated HER2, EGFR, MEK1, and Raf-1 led to a marked decrease in ER expression and genomic signaling (54–56). Resultant hyperactivation of p42/44 MAPK, which is downstream from these molecules, may lead to the reversible down-regulation of ER expression (57). More recent data suggest that sustained hyperactivity of HER2 signaling may eventually lead to a complete loss of ER expression as a mechanism of resistance to endocrine therapy (33). Whether this observed ER loss is permanent or potentially reversible is a matter of great clinical significance because it raises the question whether some apparently ER-negative tumors have repressed ER expression secondary to growth factor overexpression (Fig. 2). Fascinating recent observations, both clinical as well as experimental, lend support to this provocative hypothesis and suggest that some HER2-overexpressing tumors that are apparently ER negative may actually revert to ER positivity after treatment with anti-HER2 therapy (58, 59). Restored ER expression after anti-HER2 therapy may provide an alternative tumor survival mechanism and drive resistance to this form of therapy. Most importantly, however, restoration of ER expression may create a novel opportunity to use endocrine therapy in patients who may not have been originally considered as candidates for such intervention. These observations further emphasize the complexity of interaction between the ER and

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HER pathways and its clinical significance for treatment of women with breast cancer.

Summary and Future Perspectives

Recent progress in understanding ER biology and function has revealed complex signaling interactions between ER and other signal transduction pathways. Specifically, the intimate crosstalk between ER and the EGFR/HER2 pathways may contribute to endocrine therapy resistance and probably also to anti-HER therapy resistance. It may therefore be critical to examine other molecular features of a tumor besides ER when deciding on endocrine therapy for patients with breast cancer. Furthermore, simultaneous targeting of specific signaling pathways in addition to endocrine therapy may be necessary to maximize patient benefit, and studies testing such combinations are either currently ongoing or in planning. These and future studies must include examination of molecular biomarkers in response to treatment and upon disease progression to help further refine our therapeutic options to treat breast cancer.

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