Coregulator Expression and Breast Cancer: Improving the Predictive Power of Estrogen Receptor α

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Introduction
For more than 20 years, ERα expression has served to predict which breast cancer patients will benefit from endocrine therapy. The antiestrogen tamoxifen has been the most common endocrine agent used to treat all stages of ERα-positive breast cancer and has also proven successful in the prevention of breast cancer in high-risk women (1). However, most ERα-positive breast cancer patients that respond to tamoxifen therapy develop resistance. This can enable tumors to resume growing and disease to recur. This is a serious clinical problem, and the predictive factors and mechanisms of acquired tamoxifen resistance are not clear. In most cases, resistance is not associated with loss of ERα expression, and mutations in the receptor are very rare (2). It has been hypothesized that one mechanism of tamoxifen resistance might result from changes in ERα association with coregulator proteins because of alterations in their expression levels and activities. There is a need to identify predictive factors for response to tamoxifen therapy and to understand the mechanisms of acquired tamoxifen resistance to select the most effective therapy for ERα-positive breast cancer patients.

ERα belongs to a superfamily of nuclear receptors that function as ligand-activated transcription factors. This receptor mediates the effects of estrogens, which include proliferation and differentiation in reproductive tissues and have been linked to the pathophysiology of breast cancer. Two forms of the ER have been identified, α and β. However, a role for ERβ in breast cancer has not been defined. Upon binding ligand, ERα can modulate transcription by binding to the regulatory region of target genes directly through specific DNA sequences called estrogen response elements or indirectly through other DNA binding transcription factors. The receptor interacts with coactivators or corepressors to enhance or repress transcription, respectively. Transcriptional activation by ERα is associated with the recruitment of coactivators, including SRC-1, AIB1, TIF2, CBP/p300, and p/CAF (3). Some of these coactivators have histone acetyltransferase activity and can thereby modify chromatin structure to allow the basal transcriptional machinery to interact with promoter regions and enhance transcription.

The transcriptional activity of ERα can be modified by selective ER modulators. These compounds such as tamoxifen behave as estrogens in certain tissues and antiestrogens in others. Tamoxifen can act as an antiestrogen by competing with estrogen for binding to the ligand binding domain of ERα and inducing an alternative structural conformation that blocks coactivator interaction (4). In mammary cells, where tamoxifen acts as an antagonist, it induces the association of ERα with the corepressors NCOR1 and SMRT and histone deacetylases instead of coactivators (5). In contrast, tamoxifen treatment is associated with the recruitment of coactivators to certain ERα target genes in endometrial cells where it acts as a partial agonist (5). Changes in the expression levels of ERα coactivators and corepressors have been implicated in tamoxifen resistance (6). Thus, coregulator expression levels in target tissues may predict the response to tamoxifen.

In this issue of “Clinical Cancer Research,” Girault et al. (7) analyzed the expression of ERα coregulators in breast tumor samples from patients after surgery and before adjuvant treatment with tamoxifen alone. They asked whether there was a correlation between coregulator expression and clinical response to tamoxifen therapy to determine whether any coregulators were predictors of the response. They measured the mRNA expression levels of 16 coactivator and 11 corepressor genes using real-time quantitative reverse transcription-PCR in 14 ERα-positive breast tumors. They then additionally investigated three coactivator genes and two corepressor genes of interest that had the widest range of gene expression using a larger series of ERα-positive breast tumors. Girault et al. found that low NCOR1 expression versus intermediate or high was associated with significantly shorter relapse-free survival (7).

These findings indicate that NCOR1 may be a promising independent predictor of tamoxifen resistance in patients with ERα-positive tumors. As suggested by Girault et al. (7), the predictive value of NCOR1 needs to be validated using a prospective randomized study, including untreated breast cancer patients to determine that the outcome is influenced only in patients receiving adjuvant tamoxifen. However, the results of Girault et al. (7) complement those from earlier reports. Lavinsky et al. (8) showed that decreased NCOR1 protein expression correlated with acquired tamoxifen resistance in a mouse model of breast cancer. In addition, Kurebayashi et al. (9) found higher NCOR1 expression levels in tumors from patients without recurrence compared with patients with recurrence.

The findings of Girault et al. (7) also support the hypothesis that the expression levels of coactivators and corepressors can determine the tissue-specific response to tamoxifen. There is evidence that increased expression of coactivators such as SRC-1 can result in tamoxifen agonism (5, 10). Differences in NCOR1 levels in distinct tissues or expression relative to coactivators may also influence tamoxifen action. In this regard, tamoxifen is antagonistic in wild-type mouse embryonic fibroblasts but agonistic in NCOR1−/− mouse embryonic fibroblasts (11).
Although NCOR1 may be an independent predictor of the response to tamoxifen treatment, the expression of genes for other factors alone or together with NCOR1 may also have significant predictive value. Bieche et al. (12) previously identified ERBB2 overexpression as a marker of poor prognosis. By combining NCOR1 and ERBB2 expression status, they found that patients with the best prognosis had high NCOR1 expression and normal ERBB2 expression, indicating that analysis of two or more markers together that affect tamoxifen efficiency could provide a better prediction of response to tamoxifen therapy (9). Other coregulators studied by Girault et al. (7) showing lower ranges of gene expression or additional cofactors may also contribute to the response to tamoxifen, but the relative significance remains to be reported or determined.

Low NCOR1 expression may help to predict which patients will develop tamoxifen resistance, but questions still remain as to how the resistant phenotype is acquired and what downstream target genes may be involved in the loss of control of proliferation. Also, it is still unclear what role may be played by other possible mechanisms of resistance such as changes in the pharmacology of tamoxifen or ER-independent mechanisms that involve other interrelated signaling pathways (2). In addition, the endocrine treatment of breast cancer is an evolving area with the emergence of aromatase inhibitors as highly effective therapies (perhaps superior to tamoxifen) and the development of pure antiestrogens such as fulvestrant (Faslodex). Future studies will be needed to fully define the mechanisms of resistance and the optimal strategy for the endocrine therapy of women with ERα-positive breast cancer.

References
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