Editorial

Estrogen receptor-β: why may it influence clinical outcome in estrogen receptor-α positive breast cancer?

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See related research article by Lin *et al*., http://breast-cancer-research.com/content/9/2/R25

Abstract

In the previous issue of the journal, Lin and coworkers present data demonstrate that increased expression of estrogen receptor (ER)-β in ER-α-positive breast cancer cells antagonizes a defined group of ER-α/estrogen stimulated genes that are involved in cell cycle regulation and DNA replication. Similar expression patterns for these genes were found human ER-α positive breast tumors expressing higher levels or ER-β, and this correlated with better clinical outcome. The implications for these data, which suggest that ER-β is a positive actor and diagnostic marker for therapeutic outcome, are discussed.

The role of estrogen exposure as a risk factor for breast cancer is well-documented [1] and appears to be reinforced by the abrupt decline in new cases that correlates with cessation of widespread standardized hormone replacement therapy in post-menopausal women [2]. Estrogen exerts its biologic actions, including broad changes in gene expression, through nuclear proteins called estrogen receptors (ERs), which now include two subtypes [3]: ER-α and ER-β. Between 40% and 70% of all breast tumors express the first-identified receptor, ER-α and the discovery of ER-β highlighted potential for more complex tumor categories [2-4]. The presence of ER-α protein has been a standard criterion for instituting adjuvant therapy with antiestrogens such as tamoxifen that antagonize ER function, or more recently with aromatase inhibitors that prevent the synthesis of endogenous estrogen [4,5]. However, many patients never respond to such endocrine therapies, or they do not exhibit a sustained response [6]. Additional tumor markers that might inform therapeutic choices and increase the likelihood of positive disease outcome are clearly invaluable. Over-expression of some proteins, such as the signaling molecule p130Cas or the epidermal growth factor receptor, has been associated with therapeutic resistance to tamoxifen [7]. Conversely, expression of the progesterone receptor (PR), an estrogen-stimulated gene, presumably identifies an estrogen-sensitive cancer that might be inhibited by targeting the ER; indeed, patients with ER-positive/PR-positive tumors are more responsive to endocrine therapy than those with ER-positive/PR-negative tumors [1,8].

The report by Lin and coworkers [9] presented in the previous issue suggests that the presence of ER-β may also be indicative of more successful therapeutic responses and disease outcome in ER-positive tumors. In this case, however, ER-β itself acts by antagonizing ER-α on a very specific subset of estrogen-stimulated genes and actively prevents ER-α stimulated cell growth. UsingT47D ER-positive breast cancer cells that were engineered to inducibly over-express ER-β Lin and coworkers identified a 'signature' of estrogen-regulated genes, represented by six proteins involved in cell cycle progression and eight implicated in DNA replication, that are either attenuated or frankly antagonized by ER-β over-expression, with or without estrogen. This was accompanied by decreased cell replication. Most importantly, the investigators examined expression of ER-β in ER-α-positive primary breast tumors from a previously well described cohort of patients who had been treated with adjuvant tamoxifen therapy, and plotted gene expression against disease outcome [10]. They found that ER-β mRNA expression was negatively correlated with expression of 10 out of 12 of the tested signature genes in ER-α-positive tumors, but not ER-α-negative ones. Furthermore, patients with relatively higher levels of ER-β and lower expression of the signature gene set mRNAs had significantly improved outcomes, in terms of both disease-free and disease-specific survival, compared with the group with lower levels of ER-β and higher responsive gene set transcript levels.

ER-β was originally shown to have lower transcriptional activity than ER-α for many model promoters or on specific genes, and to antagonize ER-α actions on specific genes

ER = estrogen receptor; PR = progesterone receptor.

involved in cell cycle regulation in cell culture [2,11]. The findings of previous attempts to identify any one mRNA or protein identified in model systems as a single marker that predicts disease-free survival have not been compelling. The data presented by Lin and coworkers [9], however, suggest that groups of ER-regulated genes working together in similar pathways may bring about the desired clinical outcome, and that these *in vitro* studies may be reflected in some clinical outcomes. Furthermore, co-expression of ER-β with ER-α appears to be critical to observinig the beneficial response, although it is not currently clear whether both receptors are expressed in exactly the same cells. These responses may occur because the heterodimers formed between the two ER subtypes may identify and modulate different genes than either receptor alone [2,11]. Alternatively, the small number of ER-β-positive-only tumors identified in the literature to date might have arisen from different progenitor cells that do not require estrogen for growth and that have high expression of molecules that are associated with poorer disease outcome, such as the HER family of growth factor receptors [12].

Thus, the addition of ER-β to tumor screening, in addition to ER-α and PR, has the potential to provide interesting and important information in assessing the best therapies and disease prognosis. ER-β protein appears to be an active protector in ER-α-positive breast cancer [8]. This has raised the question of targeting ER subtypes preferentially with newly available subtype-specific ligands [13]. Interestingly, Lin and coworkers [9] found that genes encoding proteins that are active in cell proliferation and cell survival were not preferentially regulated by ER-β. However, some of these genes can be stimulated by estrogen and antagonized by some pure antiestrogens [14]. Thus, ligands or therapies that antagonize such responses to estrogen but allow antagonistic actions of ER-β may be most beneficial. As we learn more about the basic biology and pathophysiology of breast cancer, coupled with current elegant studies on molecular actions of receptors and ligands, we have reason to expect that both better diagnostics and therapies will be developed.

Competing interests

The author declares that they have no competing interests.

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