Breast Cancer RESEARCH

VIEWPOINT

Estrogen receptor degradation: a CUE for endocrine resistance?

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Abstract

Despite the undoubted success of adjuvant endocrine therapies that target the estrogen receptor pathway, not all women with estrogen receptor-positive breast cancer respond to these therapies, and many who initially respond will subsequently relapse. Deregulation of various aspects of estrogen receptor signaling has been highlighted as a mechanism of resistance and as a basis for alternative therapeutic approaches. However, a recent publication refocuses attention on the estrogen receptor itself by showing that the ubiquitin-binding CUE domain-containing protein 2 is a regulator of estrogen receptor protein degradation and a marker of endocrine resistance in breast cancer.

Background

Endocrine therapies that impair estrogen synthesis or interfere with estrogen receptor (ER) signaling are central to the standard of care for the 75% of breast cancers that are ER-positive, and these therapies, particularly the selective ER modulator tamoxifen, have made a significant contribution to the recent reduction in breast cancer mortality [1]. Many women treated with endocrine therapy will experience disease progression during therapy or subsequent recurrence of their disease, however, and so understanding the molecular basis of endocrine resistance is a priority for improving the survival of breast cancer patients [1,2].

ERα expression is a major determinant of the success of endocrine therapy: immunohistochemically detectable ERα expression in >1% of cells is sufficient to predict clinical benefit, and patients with the highest levels of ERα expression have the longest survival following endocrine therapy [3,4]. ERα levels are under complex regulation by transcription factors including multiple Forkhead family members, as well as ligand-mediated downregulation of ERα transcription and proteasomal degradation of the ERα protein [5-8]. However, the determinants of ERα levels in breast cancer are not completely understood. A recent publication identifies CUE domain-containing protein 2 (CUEDC2) as a new, and probably important, piece in this puzzle [9]. The CUE domain is a ubiquitin-binding motif, which initiates proteolytic degradation of specific targets [10].

Article

Zhang and colleagues have shown that CUEDC2 binds both the progesterone receptor (PR) and ERα, resulting in degradation of these receptors and reduction of ligand-activated gene transcription [9,11]. CUEDC2 binds PR through an interaction between the CUE domain and the N-terminal inhibitory function domain of PR, but binds ERα through an interaction between the N-terminal domain of CUEDC2 and the DNA binding domain of ERα [9,11]. The CUE domain is not necessary for ERα binding, but is necessary for ubiquitination and degradation of ERα [9].

To investigate the potential role of CUEDC2 in breast cancer, immunohistochemistry of a panel of markers including CUEDC2, ERα, PR, Ki67 and HER2 was used [9]. CUEDC2 was significantly overexpressed in breast cancer compared with adjacent normal tissue, and breast cancers with the highest CUEDC2 staining (that is, strong staining in >50% of cells) were predominantly ERα-negative and PR-negative. Both overall and in the ERα-positive subgroup, CUEDC2 expression was inversely related to ERα expression, although >20% of ERα-positive cancers had low ERα levels despite low CUEDC2 expression, or high levels of both proteins. High CUEDC2 expression was associated with reduced survival of ERα-positive patients following endocrine therapy (tamoxifen), but had no significant relationship with patient outcome in ERα-positive patients who did not receive tamoxifen therapy or in ERα-negative patients. In breast cancer cells in culture, CUEDC2 overexpression led to tamoxifen resistance. This could be reversed by co-expression of ERα, suggesting that although CUEDC2 binds multiple targets, its effects on tamoxifen sensitivity are predominately mediated through ERα.

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Viewpoint

Collectively the findings of Zhang and colleagues indicate that CUEDC2 is an important regulator of ERα expression in breast cancer, and is a mechanistically-based biomarker of response to endocrine therapy. Importantly, unlike many other biomarkers that are correlated with patient outcome following tamoxifen treatment [2], CUEDC2 appears to be specifically associated with response to therapy, rather than with an inherently poor-outcome phenotype [9]. One significant implication of this work is that ERα mRNA levels may not necessarily be a good surrogate measure of ERα protein. Overall, ERα mRNA and protein are correlated in large breast cancer series, but determination of ER status by these measures is discordant in ~10% of cases, some of which are immunohistochemically ERα-negative despite expressing readily detectable levels of ERα mRNA [12,13]. Overexpression of CUEDC2 could contribute to this discordance.

Several priorities for further investigation arise from these findings. Although regulation of ERα protein levels was necessary for the ability of CUEDC2 overexpression to confer tamoxifen resistance *in vitro*, in multivariate analysis CUEDC2 was predictive of the outcome of tamoxifen therapy independent of ERα expression [9]. ERα may thus not be the only relevant target of CUEDC2 in clinical breast cancer. Whether CUEDC2 regulates the degradation of steroid hormone receptors other than ERα and PR, and whether its expression is correlated with steroid receptor expression in hormone-dependent cancers other than breast cancer, are not known. However, CUEDC2 expression is reduced in castrate-recurrent prostate cancer, which is characterized by increased androgen receptor activity [14], suggesting CUEDC2 may also act to dampen androgen receptor signaling. In addition, there are no published data addressing regulation of CUEDC2 so it will be of significant interest to determine how the protein's expression and function are regulated in normal physiology, and to determine the mechanisms for the significant overexpression of CUEDC2 in breast cancer. Finally, it will be important to dissect the functional interrelationships between CUEDC2 and the kinase LMTK3, recently identified as a negative regulator of ERα protein degradation that is also necessary for transcription of ERα mRNA and is correlated with endocrine resistance [15].

Abbreviations

CUEDC2, CUE domain-containing protein 2; ER, estrogen receptor; PR, progesterone receptor.

Competing interests

The authors declare that they have no competing interests.

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