Breast Cancer RESEARCH

EDITORIAL

Endocrine resistance in breast cancer: new roles for ErbB3 and ErbB4

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See related research by Hutcheson *et al.*, http://breast-cancer-research.com/content/13/2/R29

Abstract

Endocrine resistance is a major limitation to the successful treatment of estrogen receptor-positive (ER^+) breast cancer, and the EGFR (epidermal growth factor receptor) and ErbB-2 receptor tyrosine kinases are involved in this process. A recent study now implicates the other two ErbB family members, ErbB-3 and -4. Exposure of ER^+ breast cancer cells to the pure antiestrogen, fulvestrant, increased levels of ErbB-3 or ErbB-4 and sensitivity to the growth-stimulatory effects of heregulin β1, a potent ligand for these receptors. Thus, the initial growth-inhibitory effects of fulvestrant appear compromised by cellular plasticity that allows rapid compensatory growth stimulation via ErbB-3/4. Further evaluation of pan-ErbB receptor inhibitors in endocrine-resistant disease appears warranted.

Introduction

A major contributor to the significant recent decline in breast cancer mortality is the use of adjuvant endocrine therapy. However, the overall efficacy of tamoxifen, aromatase inhibitors, and the pure antiestrogen, fulvestrant, is limited by *de novo* and acquired resistance. The article by Hutcheson and colleagues [1] in the previous issue of *Breast Cancer Research* further develops our understanding of the role of the ErbB family in endocrine resistance by providing new insights into the roles of ErbB-3 and -4 in modulating sensitivity to fulvestrant.

Since endocrine resistance may compromise the effective treatment and potential cure of up to 25% of all breast cancers, defining the mechanisms of endocrine resistance has been a major research focus. This body of research identifies a wide range of biological mechanisms that can confer endocrine resistance *in vitro*. These include the following: loss of estrogen receptor-alpha (ERα) expression and expression of truncated isoforms of ERα and ERβ; post-translational modification, particularly phosphorylation of ERα; increased activity of other transcription factors, including AP1 and c-Myc; deregulation of ER coactivators; and increased receptor tyrosine kinase signaling with resultant activation of the ERK and PI3K pathways and deregulation of the cell cycle, cell survival, and apoptotic machinery [2]. Although the direct relevance of these *in vitro* mechanisms to endocrine resistance in the clinic is far from clear, data accumulated in recent years provide strong evidence for a direct role for ErbB-2.

Since the initial observation that increased levels of both the epidermal growth factor receptor (EGFR/ErbB-1) and ErbB-2 activate an autocrine growth-stimulatory pathway in tamoxifen-resistant MCF-7 cells [3], a number of laboratories have replicated and extended these findings. Thus, upregulation of ErbB-1 and -2 are common features of endocrine-resistant breast cancer cells, overexpression of these receptors confers insensitivity to endocrine agents in xenograft models and in patients whose tumors overexpress these receptors, and these effects can be attenuated by therapies that target ErbB receptors in combination with tamoxifen (see [1] for references). The article by Hutcheson and colleagues [1] extends these concepts to the other two members of the ErbB family.

Potential role of ErbB-3/4

Like EGFR and ErbB-2, ErbB-3 and -4 are transcriptionally repressed by estrogen [4], and there is evidence of coregulation of the ER and ErbB pathways [5], the loss of which, in the case of ErbB-2, contributes to endocrine resistance [6]. ErbB-3 and -4 can form homodimers, but whereas ErbB-4 homodimers are active, ErbB-3 has impaired kinase activity and is active only when dimerized with another family member [7]. Whereas EGFR is activated by EGF and related growth factors, ErbB-3 and -4 are receptors for the neuregulins (NRGs) [7]. In breast cancer, the most important ligand appears to be heregulin

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β (NRG2), which, when administered to MCF-7 cells, induces a hormone-independent phenotype [8]. Although the evidence for a role for the heregulins in endocrine resistance implies a role for ErbB-3 and -4, the mechanisms are not well defined.

Hutcheson and colleagues [1] addressed this issue by exposing four ER$^+$ breast cancer cell lines to fulvestrant for 7 days. Although the responses as measured by a spectrum of cell proliferation and cell signaling endpoints showed some heterogeneity, a number of definitive conclusions were drawn. In support of earlier observations, fulvestrant treatment reduced ERα protein and ER-mediated gene expression (progesterone receptor mRNA and cyclin D1 protein) and cell proliferation (cell number and Ki67 staining) in all four cell lines. This was accompanied by increased ErbB-3 (MCF-7, T47D) and -4 (BT474, MDAMB361) protein levels (but not mRNA levels) and enhanced basal phosphorylation of both receptors and ERK1/2.

Administration of HRGβ1 alone induced the expected activation of ErbB-3 and -4, ERK1/2, and AKT, although the effects on proliferation were varied. However, in the presence of fulvestrant, all four cell lines demonstrated enhanced sensitivity to HRGβ1 as measured by ErbB receptor, ERK1/2, and AKT phosphoryation; recovery of cyclin D1 expression; and enhanced proliferation. Notwithstanding some differential effects in the four cell lines, the data are strongly supportive of the authors' conclusions that antihormones, while inducing potent growth-inhibitory activity in ER$^+$ breast cancer cells, simultaneously induce and activate growth factor pathways that override the initial response and render the cells refractory to the inhibitory effects of fulvestrant.

These data are in good agreement with those of recent publications demonstrating that ErbB-3 is activated in tamoxifen-resistant [9] and fulvestrant-resistant [10] cells and that downregulation of ErbB-3 abrogates ErbB-2-mediated tamoxifen resistance [9]. However, further work is needed to clarify the role of ErbB-4. Lykkesfeldt and colleagues [10] reported that this receptor is downregulated in fulvestrant-resistant MCF-7 cells, whereas others report upregulation in tamoxifen-resistant cells [11]. There are also inconsistent data on whether ErbB-4 is estrogen-induced [12] or antiestrogen-induced [1] and whether this is mediated at the transcriptional or post-transcriptional level.

Conclusions

The study by Hutcheson and colleagues raises a number of important issues relating to further defining mechanisms of endocrine resistance and to the identification of new therapeutic targets for future clinical testing. Their hypothesis-testing approach identifies two new targets but raises the question 'How many targets are there?' Given that ErbB-3 and -4 were upregulated at the protein level and not the mRNA level, a more global set of approaches to kinase and kinase substrate identification [13] in endocrine-resistant disease may yield a broader range of targets. Equally important is the translation of these data to the clinic. Although combinations of antihormones and growth factor inhibitors have shown great promise in experimental systems, they have, to date, been relatively disappointing in the clinic [14]. Thus, defining new mechanisms, new targets, and companion biomarkers that aid in patient selection remains a high priority. Given the current data [1], broad-spectrum ErbB inhibitors and antibodies that inhibit ErbB heterodimerization [15] warrant further detailed evaluation in endocrine-resistant disease.

Abbreviations

EGFR, epidermal growth factor receptor; ER, estrogen receptor; NRG, neuregulin.

Competing interests

The author declares that he has no competing interests.

Acknowledgments

Research in the author's laboratory is supported by National Health and Medical Research Council of Australia Program Grant 535903 and Research Fellowship 427601, the Cancer Institute NSW Program Grant 10/TPG/1-04, the Australian Cancer Research Foundation, the Petre Foundation, and the RT Hall Trust.

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Published: 20 May 2011

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doi:10.1186/bcr2878
Cite this article as: Sutherland RL: **Endocrine resistance in breast cancer: new roles for ErbB3 and ErbB4.** *Breast Cancer Research* 2011, **13:**106.