ELSEVIER

EJC Supplements Vol 2 No. 9 (2004) 45

EJC Supplements

www.ejconline.com

E13. Oestrogen receptors in metastatic breast cancer

S.A.W. Fuqua *, T. Hopp, Y. Cui

Breast Center, Baylor College of Medicine, Houston, TX 77030, USA

The oestrogen signal has long been implicated in the oncogenesis and progression of breast cancers. The biological effects of oestrogens are mediated through at least two oestrogen receptors, ER's α and β, which belong to the superfamily of nuclear hormone receptors. The traditional prognostic assays, as well as the recently developed cDNA array techniques, have demonstrated that ERα is a biomarker predicting favourable disease outcome and treatment response. However, data now suggest that the dysregulation of ERα coregulators, as well as the presence of an oestrogen hypersensitive K303R ERα mutation [1] are also important in breast tumour progression. Thus, dysregulation of components of ERα signalling could serve as prognostic markers associated with a worse prognosis later in the disease process.

The identification of ERβ in 1996 raised the question as to its role in breast cancer progression. The DNA-binding domain of ERβ is almost identical to that of ERα, and ERβ exhibits extensive regions of similarity to ERα in the ligand-binding domain Furthermore, ERβ is similarly activated by oestrogens and inhibited by anti-oestrogens, such as tamoxifen. Although studies show that ERβ is indeed expressed in most human breast tumours, its involvement in breast cancer progression remains controversial. One study suggested that expression of ERβ is associated with lymph node-positive and higher-grade tumours [2], while others have shown that ERβ expression is associated with node-negative and lower-grade cancers [3]. Thus, there is no current consensus regarding the clinical value of ERβ measurements in breast cancer. To assess the role of ERβ in breast cancer, we therefore conducted an immunoblot analysis with an ERβ-specific antibody in 305 axillary node-positive tumours with clinical follow-up. We found no significant associations between ERβ expression and ERα, progesterone receptor (PR), and other factors related to clinical outcome, such as tumour grade, age, and proliferation, or two biomarkers of tamoxifen resistance, the growth factor receptor HER-2 and the ER coactivator, AIB1. ERβ expression was not a significant prognostic factor in untreated patients. However, given the relationship between the two ERs, we also analysed the predictive value of ERβ in tamoxifen-treated patients. We explored multivariate Cox regression analysis of disease-free survival (DFS) and overall survival (OS). Our analyses revealed that patients with lower ERβ values were approximately 2 times more likely to relapse than patients with higher ERβ values, suggesting that ERβ is an independent predictive factor for DFS in tamoxifen-treated, node-positive patients. Similar results were obtained for OS in the treated group. These data suggest that breast cancers expressing low levels of ERβ may be resistant to tamoxifen treatment.

References

1. Fuqua SAW, Wiltschke C, Zhang QX, Borg A, Castles CG, Friedrichs WE, Hopp T, Hilsenbeck S, Mohsin S, O'Connell P, Allred DC. A Hypersensitive estrogen receptor-α mutation in premalignant breast lesions. *Cancer Res* 2000, **60,** 4026–4029.
2. Jarvinen T, Pelto-Huikko M, Holli K, Isola J. Estrogen receptor β is coexpressed with ERα and PR and associated with nodal status, grade, and proliferation rate in breast cancer. *Am J Pathol* 2000, **156,** 29–35.
3. Dotzlaw H, Leygue E, Watson P, Murphy L. Estrogen receptor-β RNA expression in human breast tumor biopsies: relationship to steroid receptor status and regulation by progestins. *Cancer Res* 1999, **59,** 529–532.

*Corresponding author. Tel.: +1 713 7981670; fax: +1 713 7981673.
E-mail address: sfuqua@breastcenter.tmc.edu (S.A.W. Fuqua).

doi:10.1016/j.ejcsup.2004.08.012