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AKT signalling implicated in failure of endocrine therapy

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Keywords

AKT, breast cancer, endocrine resistance, phosphorylation, survival

Context

Acquisition of endocrine resistance is a persistent problem in oestrogen receptor (ER) positive breast cancer. This phenomenon is likely to be underpinned by signalling mechanisms that enhance cell survival and proliferation. PI3 kinase/AKT signalling, which lies downstream of tyrosine kinase receptors including c-erbB2, can phosphorylate ER in a hormone independent manner and protect breast cancer cells from tamoxifen-induced apoptosis *in vitro* (see Additional information [1]). However, the contribution of this pathway to endocrine resistance *in vivo* is currently unknown. This immunocytochemical study begins to address the impact of AKT protein and its phosphorylation (pAKT) in 93 breast cancer patients treated with endocrine therapy, monitoring these parameters versus tumour clinicopathology and disease-free survival.

Significant findings

In total, 54% of tumours proved pAKT positive. pAKT was an independent predictor of distant recurrence, with a fivefold increased risk for pAKT positive patients. There was no parallel prognostic value for the AKT protein. pAKT was not associated with ER, PgR, bcl-2, c-erbB2, nodal status or tumour size. However, pAKT directly correlated with stromal heregulin ?1 content, perhaps confirming paracrine influences driving AKT signalling. An inverse association was noted with S-phase fraction (SPF). Further analysis revealed that a low SPF was prognostically favourable only when tumours were pAKT negative, the authors suggested that pAKT may promote distant relapse by a cell survival (rather than proliferative) mechanism. The authors conclude that AKT activation may have prognostic relevance in breast cancer.

Comments

This article demonstrates an association between AKT phosphorylation and relapse with distant metastasis during endocrine therapy, implicating AKT signalling in the failure of endocrine therapy. Additional supportive data for AKT activation in adverse clinical breast cancer phenotypes have also recently been obtained by (see Additional information [2]). Since some expected associations were absent in the present study (e.g. correlation with c-erbB2 overexpression {see Additional information [3]}), it is essential that larger patient numbers are examined in order to fully validate this hypothesis. Moreover, it remains to be answered whether AKT signalling initiates endocrine resistance *in vivo* via an ER activation mechanism. Such studies in clinical material should now be feasible using phosphorylation state-specific antibodies available for key sites within the ER protein.

Methods

Clinical samples, flow cytometry, immunohistochemistry, phospho-specific antibody

Additional information

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