

Active *c*-Src has prognostic and therapeutic value in ER-negative breast cancer

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Background. Approximately 33% of newly diagnosed breast cancers lack ER and these tend to have a worse prognosis as compared to ER-positive breast cancers. Therapeutic options are limited as they are not responsive to antihormonal therapy and often develop resistance to chemotherapies. We have recently shown that activation of the nonreceptor tyrosine kinase protein *c*-Src leads to the accelerated ER degradation in ER-negative breast cancers. This study performs an immunohistochemical analysis of activated *c*-Src in a large cohort of primary human breast carcinomas to a) assess its prognostic significance and b) correlate its relationship to the ER status of breast cancers.

Methods. A total of 916 patients with breast cancer diagnosed between 1987 and 1997 had clinicopathological data and paraffin-embedded tumor tissues for the study. Tissue microarrays were constructed. A four point scoring system based on immunostaining intensity was used to grade the levels of active phosphorylated *c*-Src. Grading was done by one pathologist. Statistical analysis was used to assess the prognostic significance of activated *c*-Src and its relationship to other prognostic variables.

Results. Median follow-up was 7.31 years. Active *c*-Src grade was inversely correlated with ER status ($p=0.004$) and predicted for treatment with chemotherapy ($p=0.002$) and lack of treatment with Tamoxifen ($p=0.007$). Patients with greater levels of *c*-Src tended to be younger ($p=0.004$) and had higher Bloom Richardson scores for their tumors ($p=0.004$). Higher levels of *c*-Src also predicted for shorter timing to distant recurrence ($p=0.01$) and shorter timing to death ($p=0.04$). There was a trend towards a shorter timing to regional recurrence with higher levels of *c*-Src but the relationship was not statistically significant ($p=0.08$).

Conclusion. This study supports the hypothesis that the presence of active, phosphorylated *c*-Src contributes to the development of ER-negative status in breast cancers. The presence of *c*-Src also is associated with other poor prognostic factors and contributes to a worse prognostic outcome. This study suggests that *c*-Src inhibitors may be a novel therapeutic strategy for the treatment of ER-negative breast cancers.