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FOXP1 Expression Correlates with Better Prognosis in Invasive Breast Cancer Including the ER-Positive Luminal Subtype

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Background: Fork head box P1 (FOXP1) is a FOX family transcription factor influencing ERα;-regulated transcription by interaction with the ERα; related pioneer factor FOXA1. Altered FOXP1 expression is seen in breast and prostate cancers. This study investigated FOXP1 at the protein level in breast cancer (BC) and examined associations with clinicopathological and molecular features.

Methods: FOXP1 mRNA expression was investigated in the METABRIC BC cohort (n=1980) and validated using online expression datasets [bc-GenExMiner v4.0]. Protein expression was studied in a well characterised BC primary series (n=621) using immunohistochemistry and correlations made with clinicopathological parameters and outcome.

Results: High FOXP1 mRNA and protein expression was significantly associated with low grade, low NPI, positive ER/PR status, lobular BCs, low Ki67 and negative Her2 status ($p<0.001$). Within PAM50 subtypes, high FOXP1 expression was associated with Luminal A BCs and good prognosis integrative clusters (IC3 and IC8). Nuclear FOXP1 (n-FOXP1) protein positively associated with luminal markers:CARM1, RERG and FOXA1 ($p<0.05$). Negative association with PIK3 ($p=0.023$) indicates a possible dual role whereby n-FOXP1 reduces EGFR-mediated ligand-independent ER activation, but enhances AKTmediated activation. Positive correlations with GATA3, STAT3 and CDC42 ($p<0.001$), suggest interacting pathways. On univariate analysis, n-FOXP1 overexpression showed better long term outcome in the whole cohort and ER+ subgroups ($p<0.05$). Pooled FOXP1 gene expression data in the ER+ external validation cohort showed similar association with better outcome even when adjusted for NPI/proliferation ($p<0.001$).

Conclusions: Higher n-FOXP1 correlated with low grade ER positive BCs and spelt better prognosis with increased long-term survival. The marker may be helpful to distinguish between good versus poor prognosis luminal A tumours.

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