Gene expression profiling identified FYN as important in tamoxifen resistance and a predictor of early recurrence in patients treated with endocrine therapy

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To elucidate the molecular mechanisms of tamoxifen resistance in breast cancer, we performed global analysis of gene expression, miRNA, methylation, and proteomics. Our gene array analyses identified 366 genes with altered expression in 4 tamoxifen-resistant (TamR) vs. the parental tamoxifen-sensitive MCF-7/S0.5 cell lines. Most of these genes were functionally linked to cell proliferation and death, and include FYN, PRKCA, ITPR1, DPYD, DACH1, LYN, GBP1 and PRLR. Treatment with FYN-specific small interfering RNA or a SRC family kinase inhibitor reduced the growth of TamR cell lines, while exerting no significant effect on MCF-7/S0.5 cells. Overexpression of FYN in parental tamoxifen-sensitive MCF-7/S0.5 cells resulted in reduced sensitivity to tamoxifen treatment, demonstrating growth- and survival- promoting function of the FYN protein in MCF-7 cells. FYN knockdown in TamR cells led to reduced phosphorylation of 14-3-3 and Cdc25A, suggesting that FYN, by activation of important cell cycle-associated proteins, may overcome the anti-proliferative effects of tamoxifen. Evaluation of the subcellular localization of FYN in primary breast tumors from 2 cohorts of endocrine-treated ER+ breast cancer patients, showed that membrane-associated expression of FYN in the primary breast tumor was significantly associated with increased metastasis-free (p<0.04) and overall survival (p<0.004) independent of tumor size, grade or lymph node status. This indicates that FYN may be an important novel biomarker of response to endocrine therapy. These data and other examples from our global omic analysis will be presented.