Constitutively activated STAT3 is predictive for trastuzumab resistance in primary HER2 positive breast cancer

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The likelihood of recurrence in patients with breast cancer who have HER2 positive tumors is relatively high, although trastuzumab is remarkably effective drug in this setting. Signal Transducer and Activator of Transcription 3 protein (STAT3), a transcription factor that is persistently tyrosine phosphorylated (P-STAT3) in response to numerous oncogenic signaling pathways, inhibits anti-tumor immunity and activates downstream proliferative and anti-apoptotic pathways. We hypothesized that specimens expressing P-STAT3 will confer trastuzumab resistance and thus predict resistance to trastuzumab therapy. By integrating protein (reverse phase protein array) and gene expression data from 95 HER2 positive breast cancers treated with trastuzumab in the adjuvant setting, we show that a P-STAT3 associated gene signature (P-STAT3-GS) is able to predict P-STAT3 status in an independent dataset (TCGA) (AUC = 0.78, p = 0.01), suggesting a characteristic set of STAT3 dependent induced changes in HER2 positive cancers. High P-STAT3-GS tumors were associated with trastuzumab resistance (log rank p = 0.49). These results were confirmed in the setting of the fin-HER prospective randomised controlled study, where the effect was especially prominent in ER negative tumors (interaction test p = 0.02). Of interest, constitutively activated P-STAT3 tumors were associated with loss of PTEN (r = -0.4, fdr = 0.025), elevated IL6 (r = 0.4, p = 4.72e-05) and stromal reactivation. In conclusion this study provides compelling evidence for a link between P-STAT3 and trastuzumab resistance in HER2 positive primary breast cancers. Our results suggest that addition of agents targeting the STAT3 pathway may provide valuable addition to trastuzumab for treatment of HER2 positive breast cancer.

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