Expression of HER2 in Breast Cancer Promotes a Massive Reorganization of Gene Activity and Suggests a Role for Epigenetic Regulation

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Amplification and expression of the HER2/ErbB2 oncogene in breast cancer occurs in 25-40% of cases and is associated with aggressive disease [1-4]. HER2/ErbB2 is a trans-membrane tyrosine kinase of the EGF (Epidermal Growth Factor) receptor family. The receptor readily dimerizes leading to autophosphorylation and activation of heterodimer partners [5-6]. These partners include EGF/ErbB1/HER1, HER4 and especially HER3 [5-7]. The activated receptors in turn recruit adaptor proteins which sequester substrates for downstream activation. HER2 signals through at least four major pathways including the Map kinase, PI3K/Akt, Phospholipase C, and STAT pathways [8-11]. The Map kinase pathway leads to the activation of genes that promote cell proliferation. PI3K/Akt promotes down regulation of several intermediates of apoptosis thereby promoting increased cell survival. Together these effects provide a potential mechanism for the oncogenic role of HER2.

An important landmark in breast cancer therapy was the development of the humanized monoclonal antibody, Herceptin/Trastuzumab, directed against the extracellular portion of HER2. However, in spite of advances in targeted therapy and good responses with combined anti-HER2/chemotherapy approaches, diverse mechanisms of resistance to treatment are apparent in breast cancers with amplified HER2 [12] and recurrence is common. A durable therapy has been elusive.

Detailed expression analysis studies have provided lists of potential genes whose transcript levels are influenced by HER2 [13]. This information is vital for understanding resistance, for devising new treatments, and for understanding how the aggressive properties of HER2+ breast cancer are achieved. We studied MCF7 breast cancer cells that either expressed large amounts of active HER2 or did not express HER2, as well as breast cancer cell lines with naturally amplified HER2; BT474 and MDA453. We performed whole genome expression analysis using U133 plus 2 arrays with ~54,000 probe sets. We compared these data to the distribution of RNA Polymerase II (POL II) binding in all three cell lines and gave a correlation coefficients of 0.74 – 0.90 (p < 0.01) with the array data.

Approximately 55 of the 734 genes are known to be involved in breast cancer including 12 of the 92 genes differentially regulated with HER2 expression. 38 genes of 734 have been implicated in HER2 function including 12 of the 92 genes [15-17]. The rest are candidates as novel HER2-regulated genes.

MetaCore Pathway analysis was used to look for networks among the 734 genes. Significantly enriched groups included the estrogen receptor, the progesterone receptor, and the androgen receptor–associated networks as previously reported in breast cancer [18-20]. Many genes were associated with stem cell and progenitor cell control as indicated by networks centered on NFkB, OCT3/4, and Nanog. These three overlapping networks account for 207 genes out of 734 (28%) and include 20 out of 93 differentially transcribed genes. Thus, the role of stem cells proliferation in HER2-regulated breast cancer is highly suggested. This is consistent with the observations HER2-dependent growth in cell culture and in vivo models [12, 21-23]. Our data revealed up regulation of DNMT3A and HDAC2 in HER2+ cells, which is of particular interest because of their potential global epigenetic effects in breast cancer [24, 25].

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The approach we have taken here allowed the identification of a large number of genes that are transcriptionally altered with changes in HER2 expression, and also genes that are changed in their potential for transcription via changes in POL II binding and positioning within the gene.

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