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Blockade of ErbB-2 Nuclear Function Induces the Interferon Signaling Pathway in Breast Cancer Models Resistant to Trastuzumab

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ErbB-2, a member of ErbB family of receptor tyrosine kinases, is a key oncogenic driver in breast cancer. Despite clinical efficiency of ErbB-2-targeted therapies (trastuzumab, TZ), resistance to drugs is a major issue in the clinic. While ErbB-2 is mainly a plasma membrane-bound receptor, it also migrates to the nucleus (NErbB-2) where it can act as a transcription factor or coactivator. We previously reported that NErbB-2 is a major proliferation driver in TZ-resistant breast cancer. To investigate the NErbB-2 dependent transcriptome, RNAseq was performed using a TZ-resistant breast cancer model (JIMT-1 cells) with high constitutive levels of NErbB-2. JIMT-1 cells were transfected with an ErbB-2 nuclear localization domain mutant (hErbB-2ΔNLS), which also acts as a dominant-negative inhibitor of endogenous NErbB-2 migration. Exclusion of ErbB-2 from the nucleus resulted in up-regulation of 280 genes and down-regulation of 33 genes. Functional analysis revealed that NErbB-2 blockade enriched the expression of genes involved in type-I interferon (IFN) signaling pathway. IFNB1 and its downstream effectors OAS2 and TRIM22 were among the top up-regulated genes. In an independent breast cancer model (i. e., HCC-1569 cells), exclusion of NErbB-2 from the nucleus also induced expression of these genes. Blockade of NErbB-2 localization by injection of the hErbB-2ΔNLS mutant into JIMT-1 tumor xenografts significantly inhibited in vivo tumor growth and induced mRNA expression of IFNB1, OAS2 and TRIM22. Interestingly, blockade of NErbB-2 localization by treatment with Retro-2, an inhibitor of the retrograde transport, showed similar effects consistent with modulation of the IFN signaling pathway by NErbB-2. Bioinformatic analyses showed that both the promoter and the coding region of the IFNB1 gene contain ErbB-2 associated sequences (HAS sites). ChIP-PCR analyses revealed ErbB-2 recruitment to the HAS sites of the IFNB1 promoter and coding regions in normal growth conditions. Transfection of JIMT-1 cells with the hErbB-2ΔNLS mutant abolished the recruitment of ErbB-2 at the IFNB1 gene and also caused an increase in histone H4 acetylation, a marker of active gene transcription. NErbB-2 immunostaining in a cohort of 32 primary invasive ErbB-2-positive breast carcinomas treated with TZ revealed that NErbB-2 expression correlated with a poor disease-free survival. While this cohort is small, the findings suggest that NErbB-2 could be used as a biomarker of poor response to TZ in the clinic. In summary, our findings indicate that NErbB-2 drives the growth of TZ-resistant breast cancer cells via transcriptional repression of the IFNB1 signaling pathway, and highlight NErbB-2 as a therapeutic target and biomarker in TZ-resistant breast cancer.

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