Cross-talk between HER2 and TGF-BETA-Signaling Pathways in the Development of Trastuzumab Resistance

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Overexpression of HER2 is present in about 20-30% of breast cancer tumors. HER2 sends growth signals from the cell membrane to the nucleus and contributes to the accelerated proliferation of breast cancer cells. Trastuzumab/Herceptin is an antibody that binds to the HER2 receptor and prevents downstream signaling and is standard care for patients with HER2 positive breast cancers. However, about 60 percent of patients develop resistance to the drug. The molecular basis for this resistance is still mostly unknown. The TGF-b signaling pathway has been hypothesized to play a role in the resistance to trastuzumab, particularly downstream where crosstalk between the HER2 and TGF-b signal transduction pathways is present. Utilizing HER2 antibody resistant cell lines that overexpress HER2 (MMTV-neu) in conjunction with a downregulated type II TGF-b receptor (TßRII) (MMTV/DNIIR), we aim to elucidate the mechanism of interactions between HER2 and TGF-b signaling pathways in the development of trastuzumab resistance and identify potential alternative treatments for HER2 positive cancer. Understanding the mechanism of resistance is critical for the development of strategies to prevent or overcome resistance in addition to identifying new targets for therapeutic intervention.

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