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RTK signaling in therapeutic resistance of erbB2-targeted therapy

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Gene amplification/over-expression of *erbB2* (*HER2*/*neu*) is observed in approximately 25-30% of invasive breast cancers and significantly associated with a worse prognosis. ErbB2-targeted therapies, including trastuzumab (or Herceptin) and lapatinib (or Tykerb) have been successfully used in breast cancer patients with erbB2-positive tumors. However, both *de novo* and acquired resistance to these agents frequently occurs, representing a significant clinical problem. Our recent studies revealed a co-expression of three receptor tyrosine kinases (RTKs), erbB2, erbB3, and the insulin-like growth factor-I receptor (IGF-IR), in both trastuzumab-resistant and -sensitive breast cancer cells, and an enhanced activation of the downstream signaling in the resistant cells. The three RTKs actually interacted with each other to form a heterotrimeric complex only in the trastuzumab-resistant breast cancer cells. Specific knockdown of either erbB3 or IGF-IR expression was able to re-sensitize the resistant cells to trastuzumab-mediated inactivation of downstream signaling and growth inhibition. Interestingly, the trastuzumab-resistant sub-lines also exhibited refractoriness to lapatinib. While knockdown of erbB3 dramatically re-sensitized the cells to lapatinib-induced apoptosis, specific knockdown of IGF-1R did not alter the cells' responsiveness to lapatinib. Moreover, a specific inhibitor of Akt, but not Src, significantly enhanced lapatinib-mediated anti-proliferative/anti-survival effects on the trastuzumab-resistant cells. These data indicate that erbB3 signaling is critical for both trastuzumab and lapatinib resistances mainly through activation of the PI-3K/Akt pathway, whereas IGF-1R-initiated Src activation results in trastuzumab resistance without affecting lapatinib sensitivity. Our findings may facilitate the development of precision therapeutic regimens for erbB2-positive breast cancer patients who become resistant to erbB2-targeted therapy.

Biography

Bolin Liu is an Associate Professor at the Department of Pathology, School of Medicine, University of Colorado Anschutz Medical Campus. He received extensive Post-doctoral training in the Department of Experimental Therapeutics at MD Anderson Cancer Center from 1998-2002. Since becoming an independent investigator in 2007, he has focused on studying the role of erbB3 in breast cancer development. The main research program in his laboratory is to understand the biology of receptor tyrosine kinase (RTK) signaling in drug resistance and tumor metastasis, and to identify novel approach overcoming the resistance and enhancing therapeutic efficacy in cancer treatment.

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