506a Altered Egfr Trafficking and Signaling in Iressa-Sensitive Human Cell Lines

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The small-molecule tyrosine kinase inhibitor Iressa belongs to a class of therapeutics designed to interrupt aberrant signaling by ErbB receptors (e.g., EGFR/ErbB1, HER2/ErbB2) in cancer. Recently, a strong correlation between patient response to Iressa and presence of certain EGFR mutations was identified, however the basis of this sensitivity and the effects of the mutant EGFR are not fully understood. To gain quantitative, mechanistic understanding of why these mutations correlate with Iressa response, we employed a systems approach for investigating receptor trafficking, intracellular signaling, and cell death response in a panel of cell lines bearing wild type and mutant EGFR. Measurements of EGFR internalization revealed a striking pattern of lowered internalization rate in Iressa-sensitive lines, whether EGFR was present as wild type or mutant. By probing phosphorylation of key kinases using a high-throughput immunofluorescence technique, we demonstrated differences in downstream signaling of sensitive and insensitive cell lines consistent with their differential receptor trafficking. We also showed that Iressa more potently inhibits signaling in cells whose survival is more sensitive to Iressa treatment. Experimental results will be interpreted in the context of a mathematical model for reducing data dimensionality and deciphering key signaling determinants in the cell death decision process. Results of this work portend enhanced prediction of patient response to particular therapeutic regimens and development of design principles for second generation therapies.