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Abstracts

CS-05. MUTATION SPECIFIC FUNCTIONS OF EGFR RESULT IN A MUTATION-SPECIFIC DOWNSTREAM PATHWAY ACTIVATION

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BACKGROUND: EGFR is frequently mutated in various types of cancer. Although all oncogenic mutations are considered activating, different tumor types have different mutation spectra. It is possible that functional differences underlie this tumor-type specific mutation spectrum. METHODS: We have determined whether specific mutations in EGFR (EGFR, EGFRvIII and EGFR-L858R) have differences in binding partners, differences in downstream pathway activation (gene expression and phosphoproteins), and have functional consequences on cellular growth and migration. RESULTS: Using biotin pulldown and subsequent mass spectrometry we were able to detect mutation specific binding partners for EGFR. Differential binding was confirmed using a proximilty ligation assay and/or Western Blot for the dedicator of cytokinesis 4 (DOCK4), UDP-glucose glycoprotein glucosyltransferase 1 (UGGT1), MYC binding protein 2 (MYCBP2) and Smoothelin (SMTN). We also demonstrate that each mutation induces the expression of a specific set of genes, and that each mutation is associated with specific phosphorylation patterns. Finally, we demonstrate using stably expressing cell lines that EGFRvIII and EGFL858R display reduced growth and migration compared to EGFR wildtype expressing cells. CONCLUSION: Our results indicate that there are distinct functional differences between different EGFR mutations. The functional differences between different mutations argue for the development of mutation specific targeted therapies.