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Characterization of the effects of EGFR tyrosine kinase inhibitors on intracellular signal transduction in colorectal carcinomas

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The epidermal growth factor receptor (EGFR) is overexpressed in 30-90% of colorectal carcinomas. It plays an important role in the regulation of proliferation, differentiation and survival. Therefore, EGFR targeting therapies have a high potential in reducing tumor growth. As only a certain fraction of colorectal cancer (CRC) patients responds to EGFR targeting therapies, it is necessary to stratify patients prior to treatment. This requires predictive biomarkers which are so far not available for the tyrosine kinase inhibitors erlotinib and gefitinib in CRC. In order to identify predictive biomarkers, it is essential to gain a better understanding of the molecular background of erlotinib and gefitinib resistance. The focus of this work was to analyze the effects of EGFR inhibition on key signal transduction pathways downstream of EGFR in order to reveal potential molecular bypass routes. To this end, cellular CRC models were first characterized concerning their erlotinib and gefitinib sensitivity and also concerning the mutation status of common oncogenes. The *KRAS* mutation was found not to be predictive for erlotinib or gefitinib resistance in the cellular CRC models. This was subsequently confirmed in patient-derived xenograft models. The *BRAF* V600E mutation however, was observed to potentially contribute to erlotinib resistance in one cellular model. Erlotinib and gefitinib sensitivity were not associated with the EGFR expression level or the inhibition of MAPK and PI3K/AKT signaling. In contrast to this, the insulin-like growth factor 1 receptor (IGF-1R) was activated upon EGFR inhibition in erlotinib and gefitinib resistant cell lines, whereas this effect was associated with an increased basal EGFR expression level. Based on these findings as well as the literature, it is likely that IGF-1R signaling acts as bypass route when EGFR is inhibited. This hypothesis was supported by the observation that combinatorial EGFR and IGF-1R inhibition had beneficial effects compared to single EGFR or IGF-1R inhibition. Furthermore, this study revealed that the EGFR / IGF-1R crosstalk can be triggered by both, EGFR and IGF-1R inhibition. In summary this study found further evidence for the EGFR / IGF-1R crosstalk to be involved in resistance toward EGFR tyrosine kinase inhibitors and contributes to an improved understanding of the effects of EGFR and IGF-1R inhibition on intracellular signal transduction. To improve the therapy of colorectal cancer patients, a better molecular stratification, which accounts for the heterogeneity of colorectal carcinomas, is needed.