

P005 K-Ras-mediated signal transduction in human pancreatic carcinoma cells
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Mutationally activated Ras proteins occur in 90 % of pancreatic adenocarcinoma and in 30 % of human tumours, turning Ras into one of the most important human oncogenes. To analyze the influence of oncogenic K-Ras proteins on signal transduction in pancreatic carcinoma cells, we generated PANC-1 cell clones, which stably express EGFP-tagged K-Ras(G12V). Stable expression of EGFP-K-Ras(G12V) resulted in epithelial dedifferentiation of PANC-1 cells and in enhanced cell migration and invasion, but reduced cell proliferation. Although transient expression of EGFP-K-Ras(G12V) caused enhanced ERK activity, stable expression of EGFP-K-Ras(G12V) did not result in constitutive activation of ERK. However, activation of endogenous N-Ras and ERK by growth factors was maintained in these cells, suggesting that EGFP-K-Ras(G12V) is uncoupled from activation of ERK. Interestingly, EGFP-K-Ras(G12V)-expressing cells showed enhanced phosphorylation of p38 MAPK. Furthermore, EGFP-K-Ras(G12V) resulted in enhanced phosphorylation of Akt at Ser473 and Thr308. Akt phosphorylation was sensitive to LY294002, a PI3-kinase inhibitor, arguing for a linear signal transduction from EGFP-K-Ras(G12V) via PI3-kinase to Akt. Activated Akt transduces signals via mTor to p70 S6 kinase and the S6 ribosomal protein. Inhibition of PI3-kinase/Akt as well as p38 resulted in altered cell cycle progression and downregulation of K-Ras(V12)-induced cell migration of PANC-1.