Inhibition of mTOR leads to a differential activation of AKT isoforms during the PI3K-dependent feedback loop activation in human liver cancer cells

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Aberrant activation of the PI3K/AKT/mTOR signalling pathway is frequently observed in solid tumors of the liver i.e. hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC). Treatment of liver cancer patients with mTOR inhibitors is a promising new therapy. However, a dual PI3K-dependent feedback loop activation of AKT and MAPK has been described after mTOR inhibition. This may explain the limited success of mTOR inhibitor monotherapy in clinical trials. We confirmed a dose-dependent feedback activation of AKT after mTOR inhibition in HCC and CC cell lines. Isoform specific AKT kinase assays revealed that treatment of CC cells with RAD001 resulted in a strong activation of AKT2 whereas AKT1 and AKT3 showed a modest increase in activation, only. Interestingly, activation of AKT2, but not AKT1 and AKT3, was further increased at higher concentrations of RAD001. Our data indicate that the three AKT isoforms become differentially activated after mTOR inhibition. Functional analysis of mTOR inhibition in combination with isoform specific AKT knockdowns and measurements of AKT isoform activity in primary liver tumors are currently in progress.