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Meeting abstract

mTORC1 inhibition with rapamycin or LY294002 alone but not in combination leads to AKT phosphorylation via mTORC2 in melanoma cells

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Inhibition of mTOR complex 1 (mTORC1) with rapamycin leads to phosphorylation of AKT in some cancer cells with unknown biological consequences. A mechanism involving insulin receptor substrate (IRS) and phosphatidylinositol 3-kinase (PI3K) leading to increased AKT phosphorylation has been described. For melanoma, it is unknown, whether this feedback loop plays a role, although preliminary clinical data indicate poor activity of rapalogues in melanoma. Here, we report that treatment of melanoma cells with rapamycin resulted in strong and long lasting AKT phosphorylation, but had little or no effects on cell viability, cell cycle arrest or apoptosis. Combined PI3K/mTOR inhibition with LY294002 had strong effects on these parameters, but also led to increased phospho-AKT levels after prolonged treatment. In contrast to the single treatments, combination of rapamycin plus LY294002 was able to suppress AKT phosphorylation even after prolonged treatment. Inhibition of mTOR complex 2 (mTORC2) using RNAi led to reduced levels of p-AKT, also under conditions when mTORC1 was inhibited. PTEN mutant melanoma cells showed slightly increased levels of AKT phosphorylation compared to PTEN wild-type cells. Thus, our results indicate that mTORC1 inhibition with specific inhibitors such as rapamycin as well as with multi-target inhibitors such as LY294002 can lead to AKT phosphorylation in melanoma cells via mTORC2, but without significant influence on treatment efficacy in vitro.