UKE Paper of the Month May 2013

International Journal of Cancer, April 2013, PMID: 23588885

Combined targeting of AKT and mTOR using MK-2206 and RAD001 is synergistic in the treatment of cholangiocarcinoma

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ABSTRACT: Cholangiocarcinoma (CCA) is a rare, but devastating disease arising from the epithelium of intra- and extrahepatic bile ducts. There are neither effective systemic therapies nor satisfying treatment options for inoperable CCA. Histopathological and biochemical studies of CCA show frequent dysregulation of the PI3K/AKT/mTOR pathway. Therefore, we investigated the efficacy of the mTOR inhibitor RAD001 and the impact of AKT signaling following mTOR inhibition in the treatment of CCA. RAD001 significantly inhibits proliferation of CCA cell lines, however, a concentration-dependent and isoform specific feedback activation of the three AKT isoforms (AKT1, AKT2, AKT3) was observed after mTOR inhibition. Since activation of AKT might limit the RAD001-mediated anti-tumor effect, the efficacy of combined mTOR and AKT inhibition was investigated using the allosteric AKT inhibitor MK-2206. Our results show that inhibition of AKT potentiates the efficacy of mTOR inhibition both in vitro and in a xenograft mouse model in vivo. Mechanistically, the anti-proliferative effect of the pan-AKT inhibitor MK2206 in the CCA cell line TFK-1 was due to inhibition of AKT1 and AKT2, because knockdown of either AKT1 or AKT2, but not AKT3, showed a synergistic reduction of cell proliferation in combination with mTOR treatment. Finally, by using an AKT isoform specific in vitro kinase assay, enzymatic activity of each of the three AKT isoforms was detected in all tissue samples from CCA patients, analyzed. In summary, our preclinical data suggest that combined targeting of mTOR and AKT using RAD001 and MK-2206 might be a new, effective strategy for the treatment of CCA.

STATEMENT: *The PI3K/AKT/mTOR pathway is frequently activated in cholangiocarcinoma (CCA). Our interdisciplinary study demonstrates for the first time that dual targeting of mTOR and AKT synergistically inhibits proliferation of CCA cells both in vitro and in a xenograft mouse model in vivo. Mechanistically, the anti-proliferative effect of the AKT inhibitor MK2206 was due to inhibition of AKT1 and AKT2, but not AKT3. Our results open a new treatment strategy of cholangiocarcinoma by combined targeting of mTOR and AKT.*

BACKGROUND: This work was performed at the Institute of Biochemistry and Signal Transduction in the group of Prof. Manfred Jücker in close cooperation with Prof. Nashan from the Department of Hepatobiliary and Transplant Surgery, University Medical Center Hamburg-Eppendorf. It was part of the MD thesis of Florian Ewald. Our major research interest is the signal transduction in solid tumors and the development of new targeted therapy approaches for liver cancer. The project was funded by Novartis GmbH.