

P005 Role of Ser2448 in the regulation of the mammalian target of rapamycin pathway in hepatocytes

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We have previously shown that glucagon stimulates Ser2448 phosphorylation of mTOR, but inhibits phosphorylation of its downstream effectors. Interestingly, we found that another inhibitor of the mTOR pathway, the AMP-activated protein kinase (AMPK), also leads to increased Ser2448 phosphorylation when activated with 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR). As it has been shown that glucagon activates AMPK in perfused rat liver, we looked whether such mechanism was involved. However, we found that the inhibitory effect of glucagon on the mTOR pathway is not mediated through AMPK. Moreover, glucagon-induced phosphorylation of mTOR on Ser2448 is sensitive to rapamycin which is not the case for AICAR's effect.

To investigate the role of Ser2448 phosphorylation, we performed subcellular fractionations and co-immunoprecipitations in primary cultures of rat hepatocytes. We found that mTOR is present in the cytosol and in the nucleus and that the species phosphorylated on Ser2448 is predominantly nuclear. Moreover, increased phosphorylation of Ser2448 seems to correlate with increased association of RAPTOR with mTOR. Considering our data collectively, we would like to suggest that Ser2448 phosphorylation could be important for the cellular localization of and/or the function of mTOR in the nucleus and its association with its binding partners.