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Convergence of Wnt/Beta-catenin and mTOR Signaling in Liver Physiology and Hepatocellular Carcinoma

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Convergence of Wnt/β-catenin and mTOR Signaling in Liver Physiology and Hepatocellular Carcinoma

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Previous studies showed that the mechanistic Target Of Rapamycin (mTOR), a central regulator of cell growth, is activated in the early stages of preneoplastic foci development. We have also shown enhanced mTOR activity in hepatocellular carcinoma (HCC) that occurs due to cooperation of point-mutant β-catenin and hMet coexpression in liver. These signaling pathways, mTOR and Wnt/β-catenin, have been singly implicated in the pathogenesis of HCC, thus, our aim was to investigate their interactions in hepatic pathophysiology. We hypothesized that mTOR is regulated by β-catenin in hepatic physiology and pathology to contribute to HCC. To test this hypothesis, we silenced β-catenin in HCC cells to examine impact on mTOR. We utilized liver-specific β-catenin knockout (KO1) and Wnt co-receptor LRP5/6 double KO (KO2) to examine mTOR. Lastly, we examined the effect of mTOR modulation in HCC model responsive to β-catenin inhibition. β-Catenin knockdown in Hep3B cells decreased mTOR and p-mTOR, while mTOR knockdown had no impact on β-catenin. We identified phospho-mTORC1 representing the active form of mTOR to be located in pericentral hepatocytes, same location where β-catenin is constitutively active. Intriguingly, we identified absence of p-mTOR in pericentral hepatocytes in both KO1 and KO2. Lastly, we observed that the pharmacological co-inhibition of mTOR and Met in our HCC model attenuates tumor burden and increased survival. Thus, our studies provide evidence of interactions between mTOR and Wnt/β-catenin signaling in liver homeostasis and in HCC. We demonstrate that the combination of mTOR and Met inhibitors is an effective approach to reduce liver tumor burden and may represent candidate chemotherapeutic strategy for the distinct subset, which represents 10% of all HCC.