



VCU

Virginia Commonwealth University
VCU Scholars Compass

Hepatobiliary Cancers: Pathobiology and
Translational Advances

Dept. of Pathology

2017

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

Adeola O. Adebayo Michael
University of Pittsburgh, aom11@pitt.edu

Junyan Tao
University of Pittsburgh, jut24@pitt.edu

Satdarshan P. Monga
University of Pittsburgh, smonga@pitt.edu

Follow this and additional works at: http://scholarscompass.vcu.edu/hepa_cancers

 Part of the [Cancer Biology Commons](#), and the [Disease Modeling Commons](#)

© The Author(s)

Downloaded from

http://scholarscompass.vcu.edu/hepa_cancers/21

This Abstract Accepted for Presentation is brought to you for free and open access by the Dept. of Pathology at VCU Scholars Compass. It has been accepted for inclusion in Hepatobiliary Cancers: Pathobiology and Translational Advances by an authorized administrator of VCU Scholars Compass. For more information, please contact libcompass@vcu.edu.

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

Adeola O. Adebayo Michael, Junyan Tao, Satdarshan P. Monga.

Division of Experimental Pathology, University of Pittsburgh, School of Medicine, Pittsburgh PA,

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.