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Non-alcoholic steatohepatitis (NASH) is the leading cause of chronic liver disease worldwide. The pathophysiology that underlies the progression from bland steatosis to NASH, fibrosis, and **hepatocellular carcinoma (HCC)** remains largely unknown, and there are currently no FDA-approved drugs to treat NASH. The two PIs have recently published that hepatocytes (HCs) in human and mouse NASH liver have elevated levels of the transcription factor **TAZ** and that silencing HC TAZ suppresses steatosis-to-NASH fibrosis progression. We have since shown that the closely related protein **YAP** is also elevated in NASH and that HC YAP, surprisingly, *suppresses* steatosis, NASH, and fibrosis. We have also shown that HC cholesterol accumulation, a key feature of human NASH, increases HC TAZ/YAP by blocking their proteasomal degradation. Finally, we found high levels of TAZ/YAP in NASH-induced HCC, and our pilot studies show that HC-TAZ silencing prevents NASH-to-HCC progression. **The objective of this proposal is to explore the hypothesis that cholesterol-induced elevations in HC TAZ and YAP modulate the progression to NASH, fibrosis, and HCC and that TAZ may represent a therapeutic target for all disease stages**. ***Aim 1*** explores the mechanisms and consequences of how HC YAP suppresses steatosis. We will test the hypothesis that HC YAP (*a*) represses genes involved in *de novo* lipogenesis and triglyceride synthesis, in part via HC YAP-mediated decrease in PPAR□□ and (*b*) induces genes involved in fatty acid oxidation. We will then test the hypothesis that blocking HC YAP promotes NASH fibrosis via its pro-steatotic actions and possibly by increasing HC TAZ. We will also test whether forced expression of HC-YAP in early fatty liver disease can prevent steatosis and the progression to NASH. ***Aim 2*** investigates the mechanism of up-regulation of HC TAZ and YAP in NASH. We propose that proteasomal degradation of TAZ/YAP mediated by the E3 ligase TrCP is inhibited in NASH and the mechanism involves cholesterol accumulation in HCs. We hypothesize that elevation of HC membrane cholesterol alters cell signaling to block the phosphorylation of sites on TAZ and YAP required for TrCP recognition or directly inhibit TrCP itself. ***Aim 3*** explores the role of the cholesterol-TAZ/YAP pathway in NASH-induced HCC. We hypothesize that cholesterol-induced TAZ accumulation – both via cholesterol uptake and HMG-CoA reductase-mediated pathways - promotes the development of HCC in advanced NASH. We will first test if the progression from NASH to HCC can be prevented by genetic targeting of HC TAZ, as suggested by pilot data, HC YAP, and HC TAZ + YAP. We will then test the hypotheses that (*a*) cholesterol-induced HC-TAZ accelerates the NASH-fibrosis-HCC sequence; (*b*) cholesterol-induced TAZ and YAP also drive malignant transformation in tumor-initiating HC via cell-autonomous mechanisms; and (c) statins inhibit TAZ/YAP and NASH-induced HCC. Successful completion of these aims will provide critical new information to help advance therapeutic translation of our discoveries for NASH and its complications.