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A Tale of Two Complications of Obesity: Nonalcoholic steatohepatitis (NASH) and Hepatocellular carcinoma (HCC)

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Abstract

Nonalcoholic steatohepatitis (NASH) is the most common cause of chronic liver disease in developed countries and its incidence is rapidly increasing. Cirrhosis, and the dreaded complication of hepatocellular carcinoma (HCC), are the major drivers of morbidity and mortality in NASH. Conventional understanding has been that chronic liver damage leads to a cycle of cell death, regeneration and fibrosis during which HCC precursor cells undergo malignant transformation and lead to cancer initiation. This is supported by epidemiologic data which shows that cirrhosis precedes HCC in more than 90% of patients with several forms of chronic liver disease like hepatitis C and alcohol cirrhosis. But the link between fibrosis and carcinogenesis seems less definitive in patients with NASH as a sizeable proportion of NASH patients with HCC do not have significant underlying fibrosis. Several case reports and case series have pointed out this phenomenon of HCC arising in non-cirrhotic NASH (1), and a recent meta-analysis of 19 studies has shown that the prevalence of HCC in non-cirrhotic NASH was up to 38.0% (2). The mechanisms that contribute to the development of HCC in obesity in the absence of NASH and/or overt fibrosis or cirrhosis have remained unexplored. A possible mechanism to explain the role of obesity in the pathogenesis of HCC independent of NASH, was recently reported in a paper in *Cell* (3).

Graphical Abstract

Grohmann et al report that obesity contributes to NASH and HCC through independent mechanisms. The oxidative hepatic microenvironment in obesity oxidizes phosphatase T cell protein tyrosine phosphatase (TCPTP) and leads to activation of both STAT-1 and STAT-3 signaling. In mouse models of obesity and NASH, they found that obesity drives NASH via STAT-1 signaling and alternatively, promotes HCC via STAT-3 signaling. Then, they show that the attenuation of STAT-1 signaling prevents NASH but not HCC, while inhibiting STAT-3 signaling blocks HCC but not NASH. The authors conclude that there is a dissociation between STAT-1 and STAT-3 activation pathways and hence obesity may contribute to NASH and HCC through different mechanisms.

To understand the mechanisms by which obesity contributes to NASH and HCC, the authors examine the role of protein-tyrosine phosphatases. Previously, the same authors had reported that obesity induced oxidative stress in the liver inactivates protein-tyrosine phosphatases (PTPs) exacerbating insulin resistance (4). Now, in this more recent paper, they asked if NASH resulted in the inactivation of PTPs. Mice were fed normal chow or high fat diet (HFD) to promote obesity and hepatic steatosis, or choline-deficient HFD diet (CD-HFD) to promote NASH. Obesity led to PTP oxidation and inactivation resulting in activation of STAT-1 and STAT-3 pathways in NASH (CD-HFD), to an even greater extent than NAFL alone (HFD). Also, the authors found that T cell protein tyrosine phosphatase (TCPTP), was the key phosphatase of interest that was highly oxidized in the livers of obese mice with NASH versus NAFL. Hence, hepatic TCPTP oxidation in vivo, may contribute to the progressive development of NASH in obese patients.

To understand how hepatic TCPTP contributes to NASH and HCC, the authors next generated a mouse model with depletion of TCPTP in hepatocytes (C57/B6; Alb-Cre; *Ptpn2^{fl/fl}*). Compared to control mice (*Ptpn2^{fl/fl}*) that develops only hepatic steatosis when given HFD diet, TCPTP depleted mice progresses to NASH. NASH progression was confirmed by observing steatosis, hepatocyte ballooning, immune cell infiltration, liver

inflammation and increased fibrosis. Interestingly, only hepatocyte-specific TCPTP-deficient but not wild-type mice on HFD-diet develop HCC. Next, they examined how TCPTP deficiency influenced STAT1 and STAT3 pathway activation in NASH. They found that hepatocyte specific TCPTP deficiency with heterozygous loss of STAT1 (Stat1^{fl/+}) delayed NASH progression, but remarkably, had no effect on HCC. The authors further deciphered that obesity-induced activation of STAT1 promotes NASH by upregulating target genes Cxcl9 and Lnc2, which in turn recruit both T cells and neutrophils to promote inflammation and fibrosis in the liver. In contrast, HFD-fed TCPTP deficient mice with heterozygous deficiency of STAT3 (Stat3^{fl/+}) were protected from HCC development but not from NASH progression. The most likely mechanism by which STAT3 promotes HCC is via activation of the IL6-STAT-3 autocrine loop leading to malignant transformation of cancer progenitor cells. The authors conclude that activation of STAT1 signaling in obesity leads to NASH but not HCC, while STAT3 activation promotes HCC independent of NASH.

Lastly, the authors examined if their findings are seen in human obese patients. They found in human NAFLD, TCPTP was oxidized and inactivated. Further, just as seen in TCPTP deficient mice, livers of human patients with NAFLD showed activation of STAT1 signaling, and upregulation of STAT1 target genes like *CXCL9/LNC2*, compared to livers of obese patients without steatosis. Hence, the authors conclude that the phenotype seen in TCPTP deficient mice resemble human NASH and the mechanistic insights they have described are relevant to understanding risk of HCC or NASH in obese patients. Importantly, other papers support the notion that obesity activated STAT1 is pro-inflammatory and that STAT3 is a master regulator of mechanisms that contribute to major hallmarks of cancer (5, 6). However, what was not appreciated previously is that obesity leads to the inactivation of TCPTP which is the primary mechanism by which STAT1 and STAT3 are activated. Still, it remains to be determined if there are other mechanisms by which obesity activates STAT1 and STAT3 and what role known regulators of this pathway, like leptin and adiponectin, play. It is also to be noted that the authors do now show direct human evidence for the dichotomy seen in mice for separate pathways of NASH and hepatocarcinogenesis. Moreover, clearly a larger study in patients with HCC associated with non-cirrhotic NAFLD is needed, since the authors included analysis of only a limited number of human tissues.

The findings of this paper have broader public health and therapeutic implications since the authors clearly show how obesity can lead to aggressive HCC even in the absence of NASH. The American Association for the Study of Liver Diseases (AASLD) and other societies currently recommend screening for HCC only in patients with NASH who already have cirrhosis. However, the findings in this paper imply that such a strategy does not recognize the patients at risk for obesity-associated HCC. The magnitude of this health issue is growing since around three fourth of the US population will be overweight or obese by the year 2020, and a third of these obese patients are estimated to have hepatic steatosis. Even then, the low prevalence of population-attributable fraction of non-cirrhotic HCC in NAFLD makes it difficult to justify surveillance of all obese patients for HCC (7, 8). Based on this study, markers of STAT3 pathway activation may serve as potential biomarkers for obesity related HCC. Finally, the paper suggests that the inhibition of STAT1 could be a treatment for NASH and the inhibition of STAT3 for HCC. STAT3 inhibitors are, in fact, already in early clinical trials for HCC ([ClinicalTrials.gov NCT03195699](https://clinicaltrials.gov/ct2/show/study/NCT03195699)) and STAT1 inhibition needs

to be further explored for NASH. Thus, Grohmann et al have conducted an important study with significant translational relevance which offers a possible explanation for the rise of HCCs in livers of obese patients without significant inflammation or fibrosis.

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