Editorial

Dissociating nonalcoholic steatohepatitis from hepatocellular carcinoma in obesity

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Introduction

The prevalence of obesity has increased over the last decades reaching epidemic proportions: 39% of adults were overweight or obese in 2016 worldwide, according to World Health Association (https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight). Moreover, obesity is linked to metabolic syndrome (MetS) and related comorbidities, including nonalcoholic fatty liver disease (NAFLD), type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and malignancies, thus resulting in higher mortality for obese individuals (1).

NAFLD is currently considered as the most predominant chronic liver disease worldwide (2). NAFLD starts from simple steatosis (SS) that may progressively advance to nonalcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma (HCC) (3). Mortality is higher in NASH patients, owing to hepatic (i.e., cirrhosis and HCC) and extra-hepatic morbidity, including CVD and malignancies (4). Therefore, the estimated burden of NAFLD on healthcare cost and resource utilization is regarded as significant (5). Notably, despite its high prevalence, there is currently no approved treatment of NAFLD (6).

Obesity has been linked not only with the upward trend of NAFLD prevalence, but also with its more severe phenotypes, including HCC (7). By 2014, the contribution of NAFLD to HCC was 12% in a European population (8). Importantly, the prevalence of NAFLD-related HCC increased from 2.6% in 1995–1999 to 19.5% in 2010–2014, following a similar trend in overweight/obesity (from 34% to 52%, respectively) (8). NASH-related cirrhosis is not a prerequisite for HCC, since it may occur in non-cirrhotic liver (9). However, the molecular links mediating a potential dissociation between NASH/fibrosis and HCC have been poorly investigated.

Obesity-driven STAT-1 and STAT-3 signaling

Recently, Grohmann *et al.*, based on a series of elegant *in vivo* experiments, proposed that obesity leads to the development of NASH/fibrosis and HCC through different molecular pathways emanating from a common origin, namely the activation of signal transducer and activator of transcription (STAT)-1 (NASH/ fibrosis) and STAT-3 (HCC) pathways, as a result of the oxidative inactivation of T-cell protein tyrosine phosphatase (TCPTP) and, possibly, other protein tyrosine phosphatases (PTPs) (10).

The same group had previously shown that PTPs are extensively oxidized in the liver of mice that develop SS after they are fed a high-fat diet (HFD) (11). Based on that observation, they initially examined whether the hepatic oxidation of PTPs in obese mice contributes to the development of NASH and HCC. They showed that C57BL/6 mice fed a HFD (promoting obesity, IR and SS, but not NASH) resulted in increased oxidation of PTPs, including PTP1B and TCPTP; more importantly, this effect was even more evident in mice fed a mixed choline-deficient (CD)-HFD (that additionally promotes the

progression of SS to NASH) (10).

Given that PTP1B and TCPTP are negative regulators of Janus kinase (JAK)/STAT signaling, Grohmann *et al.* investigated whether oxidation of PTP1B and TCPTP induces the phosphorylation/activation of STAT-1, STAT-3 and STAT-5. They showed that STAT-1 and STAT-3, but not STAT-5, phosphorylation was increased in the livers of HFD-fed mice, with additional increment in those of CD-HFD-fed mice (10). Moreover, abolishing TCPTP expression in the hepatocytes of transgenic C57BL/6 mice (*Alb-Cre;Ptpn2*$^{fl/fl}$), which do not normally develop NASH, fibrosis or HCC, resulted in the recruitment and infiltration of T-cells in the liver and progression of SS to NASH, fibrosis and HCC (10). Next came the dissection of STAT-1 and STAT-3 roles in the development of NASH/fibrosis and HCC, respectively. Grohmann *et al.* used TCPTP-deficient C57BL/6 mice with heterozygous loss of either STAT-1 (*Alb-Cre;Ptpn2*$^{fl/fl}$*;Stat1*$^{fl/+}$) or STAT-3 (*Alb-Cre;Ptpn2*$^{fl/fl}$*;Stat3*$^{fl/+}$) to show that, following exposure to HFD, attenuation of STAT-1 signaling led to prevention of T-cell recruitment and progression to NASH, but not of HCC. Inversely, attenuation of STAT-3 signaling prevented HCC without affecting progression to NASH and fibrosis (10). In addition, analysis of liver tissue gene expression by unbiased RNA sequencing verified by targeted real-time PCR, produced STAT-specific patterns of expression associated with each particular phenotype: genes associated with T-cell recruitment (*Cxcl-9*) and fibrosis (*Acta2*, *Tgfb*) were specifically dependent on STAT-1, whereas a gene linked to tumorigenicity (*Fgl1*) was specifically associated with STAT-3. Notably, acute response and inflammation-related genes (*Saa1*, *Crp*, *Ifng*, *Tnf*) were associated with both STAT-1 and STAT-3 activation (10). Most importantly, the investigators showed that treatment of TCPTP-deficient mice with the chemical carcinogen diethylnitrosamine (DEN), which leads to the development of liver tumors in the absence of NASH/fibrosis, was accompanied by a STAT-3 signaling activation (10).

Finally, the authors validated some of their findings in humans. First, the oxidation of PTPs co-migrating with TCPTP was higher in obese with NAFLD activity score (NAS) 2-4 than in obese without steatosis (NAS =0). Second, the phosphorylation of STAT-1 and STAT-3 was increased in the livers of obese patients with NAFLD (NAS 2-4) compared with non-obese individuals. Furthermore, the expression of *CXCL9* and *FGL1* was progressively increased from obese individuals without steatosis to those with SS and even more to those with NASH (10).

Closing remarks and future directions

The study by Grohmann *et al.* is the first to provide robust evidence for the dissociation between NASH/fibrosis and HCC in obesity. This dissociation had been previously suspected from clinical studies, which had revealed the presence of HCC in non-cirrhotic NAFLD patients (9). The authors were based on the results of their previous work (11) and went forward by using a rational step-by-step investigative process and state-of-the-art methodology. Their results warrant observational clinical studies to validate their findings in obese individuals. If validated, then there are certain research and clinical implications. First, surveillance for HCC should be expanded to all obese patients with NAFLD, since HCC may occur without NASH or fibrosis. It is underlined that the surveillance for HCC is currently considered to be inadequate in NAFLD patients, a fact that delays HCC diagnosis and treatment (12). This is most likely due to the notion that NAFLD is generally a benign disease, which does not raise particular concern among health care providers and policy makers (7). Moreover, effective screening is hampered by limited knowledge of the pathways underlying the pathogenesis of HCC in NAFLD and a lack of tools needed to stratify the associated risk (12). In this regard, the Grohmann *et al.* study provides fertile ground for studies investigating the degree of oxidative inactivation of TCPTP or other effectors and mediators of STAT-3 signaling as diagnostic tools for the early diagnosis of HCC in obese individuals with NAFLD. Another possibility is the design of diagnostic tests exploiting the reported close association of *CCXL9* expression with early events in the progression of NAFLD to NASH, and, most importantly, that of *FGL1* expression to HCC. Moreover, compounds that help prevent or minimize oxidation of PTPs involved in STAT-1 and STAT-3 activation or directly inhibit STAT-3 need to enter the drug discovery/development pipeline to provide drugs that may help prevent HCC in NAFLD patients. In fact, TTI-101, an oral inhibitor of STAT-3, is at a phase I clinical trial in patients with various types of malignancy (n=30), including HCC (NCT03195699).

Yet another dimension of the findings reported by Grohmann *et al.* is the possible involvement of cytokines, adipokines and other mediators, acting via STAT-1 and STAT-3 pathways, in NASH/fibrosis and HCC development. For example, leptin, which is upregulated in obesity, was previously proposed to participate in the pathogenesis of NAFLD through a JAK/STAT-3 pathway (13,14). However, it remains to be shown whether leptin

upregulation contributes to the increased risk of HCC via the activation of STAT-3 signaling.

Although the Grohmann *et al.* study elucidated potential mechanisms promoting NASH/fibrosis and HCC, both these diseases are multifactorial, thus more than one pathogenetic mechanisms are involved in their pathogenesis. Therefore, STAT-1 and STAT-3 activation may separately promote NASH/fibrosis and HCC, respectively, but they are not expected to be the unique pathways in their pathogenesis. Thus, Grohmann *et al.* study provide evidence for HCC possibly arising without NASH/fibrosis, but it could not explain the higher rates of HCC observed in patients with more advanced NAFLD (9). Although NASH/fibrosis may not be prerequisites for HCC, still advanced fibrosis remains a strong risk factor of HCC (9). Indeed, at this point, it is hard to figure out how TCPTP inactivation could differentially affect STAT-1 and STAT-3 pathways, although one can imagine that PTPs with particular STAT-1 or STAT-3 specificity could also be involved. Also, one cannot exclude the possibility of cross-talk between different STAT pathways in the clinical setting.

In conclusion, the work by Grohmann *et al.* has opened a new range of possibilities that will keep NAFLD investigators busy for some time to come. The decoding of molecular pathways linking obesity, NAFLD and HCC is expected to reveal useful targets for the development of new diagnostic tools and medications for the specific treatment of NASH or HCC. Additionally, it has provided further molecular evidence for a major take home message: global efforts should mainly focus on the prevention of obesity (15); the interception of obesity epidemic may not only diminish its impact on the increasing rates of NASH and HCC, but will certainly have multiple-system health benefits.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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