Editorial

Molecular pathways between obesity, non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC)

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Obesity represents a major health problem worldwide. World health organization estimated that over 650 million adults were obese in 2016 and 1.9 billion were overweight (1). In the United States, the prevalence of obesity is approximately 36%, whereas it ranges from 10% to 30% in different countries (1-3) in Europe. It is well known that obesity is a strong risk factor for a number of diseases, including diabetes, hyperlipidemia, coronary artery disease, obstructive sleep apnea, chronic kidney disease, depression, and several cancers, such as breast, uterus and colorectal cancer (3).

The increased prevalence of non-alcoholic fatty liver disease (NAFLD), mainly in developed countries, has been related to the epidemic of obesity (4). NAFLD, including liver steatosis, nonalcoholic steatohepatitis (NASH), cirrhosis [with is a strong risk factor for the development of hepatocarcinoma (HCC)], affects 25–30% of people worldwide, and 90% of obese patients (4). NAFLD-associated morbidity and mortality are also increasing, including HCC, end-stage liver disease, and extrahepatic diseases such as chronic kidney disease, cardiovascular disease, and malignant disease, with major implications also in the field of liver and kidney transplantation.

The pathogenesis of NAFLD is related to multiple factors, including genetic, epigenetic, and environmental factors such as type of diet, physical activity, excess body weight, dysregulation of adipokines and hormones, insulin resistance, microbiota modifications, oxidative stress (4). The complex interaction between some or all of these factors leads to the accumulation of lipids in the hepatocytes (steatosis), which may be followed by immune cell infiltration (NASH), and fibrosis. Obesity has a crucial role in the establishment of liver steatosis, and progression to NASH. The hepatocytes, in obese patients, may store extra lipids, originating from the diet, from adipose tissue lipolysis and *de novo* lipogenesis. The subsequent lipotoxicity and glucotoxicity in the liver is characterized by the accumulation of toxic metabolites which leads to the activation of cellular dysfunction, lipoapoptosis, and inflammation (5). Another obesity-related mechanism of liver damage is the disruption of the release of adipokines, with predominance of steatogenic, fibrogenic and pro-inflammatory signals, associated to cytokines produced by immune cells infiltrating the adipose tissue (4).

Obesity has been demonstrated to be related to hepatocellular carcinoma onset and tumor progression, via molecular, immunological and neural modifications and signaling (6). The incidence of HCC, which represents 85–90% of primary liver tumors, has consistently increased in the last 20-year in developed countries, simultaneously with the obesity epidemic (7). HCC may represent a complication of NAFLD, with an estimated one-year cumulative incidence of 2.5% in patients with NAFLD-related cirrhosis (8). However, a significant proportion of patients with NAFLD will never develop HCC, and HCC is not inevitably related to NAFLD-cirrhosis or fibrosis in obese patients. It is crucial to better explore the complex relation between obesity, NAFLD, NASH, cirrhosis and HCC.

In this setting, the recent study by Grohmann *et al.* (9) published in the November, 2018 issue of *Cell*, shed an important light in the understanding of molecular mechanisms which relate obesity with NASH and HCC. The authors, studying mice models fed with standard, high

fat or choline-deficient high fat diets, and liver biopsies of obese patients with or without NASH, elucidated important molecular mechanisms in this complete and remarkable study (9). They demonstrated at first that protein tyrosin phosphatases (PTPs) oxidation may contribute to the progression of NASH and fibrosis. This finding led to the investigation of the JAK/STAT signaling. JAK/STAT signaling is a crucial pathway for the regulation of the immune response, and for the regulation of stem cells and cell identities (10). Levels of STAT-1 and STAT-3 phosphorylation increased in mice fed with high fat diet and NASH-promoting diet (9). These experimental findings were concordant with the results of liver biopsies in obese patients. The induced inactivation of STAT-1 and STAT-3 Tcell Protein Tyrosine Phosphatase (TCPTP) in the obese mice models resulted in the promotion of NASH, fibrosis, and in the development of HCC-like tumors, expressing increased Ki67, EpCAM and cytokeratin 19 (9). The transcriptome analysis showed that the TCPTP deficiency was associated with the activation of acute-phase response, JAK/STAT, and cytokine signaling pathways. STAT-1 and STAT-3 participated in the expression of genes responsible of immune response, liver regenerative response, development of NASH and fibrosis, and were identified as mediator of NASH following TCPTP inactivation (9). Repression of p-STAT-1 was associated to a "correction" of the hepatic inflammation, but not to the prevention of tumors onset, whereas STAT-3 heterozygosity repressed tumors development (9).

The study highlights the respective roles of STAT-1 signaling in inducing NASH and fibrosis and of STAT-3 in promoting HCC formation. Probably the most relevant finding is that STAT-3 signaling can drive tumor onset in a context of obesity with NAFLD, independently of the presence of NASH and fibrosis. Oxidative stress, via inactivation of the PTPs, is at the beginning of this pathological pathway; whereas STAT proteins have the role of mediator transducing cytosolic signaling and acting as transcription regulator of key genes in the immune response, cell proliferation, differentiation and apoptosis.

From a clinical point of view, the results of this study help in the understanding of the mechanisms responsible to the development of HCC in obese patient with NAFLD, who do not have NASH or fibrosis and cirrhosis. Several potential clinical implications should be emphasized.

The understanding of molecular pathways leading to development of HCC in obese patients, in the absence of NASH, cirrhosis or fibrosis, may be in the future a key factor for surveillance and early cancer detection. It can be speculated that the identification in obese patients of molecular markers related to STAT-3 signaling will help to select those patients needing HCC surveillance protocols or facilitate diagnosis of early stage tumors.

Furthermore, better understanding of molecular pathways of NASH and HCC in obese patients could in the future have a role in the development of targeted therapies. Action on the JAK/STAT signaling pathway may help to prevent or treat these conditions. A number of strategies to block STAT-3 have been developed or are in clinical trials, considering its emerging role in several cancers (11). On the other hand, research on STAT-1 inhibitors is not so developed and its role in NASH onset may push to better explore new therapeutic strategies.

Considering the obesity epidemic and the increasing number of patients affected by NAFLD, the results of the study of Grohmann *et al.* (9) appear even more relevant, because they open the way to further research that probably will influence the management of a consistent number of patients worldwide.

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Footnote

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

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