Commentary

New players in non-alcoholic fatty liver disease induced carcinogenesis: lipid dysregulation impairs liver immune surveillance

Ngoc Lan Tran, Giovanni Sitia

Division of Immunology, Transplantation and Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy

Correspondence to: Giovanni Sitia. Division of Immunology, Transplantation and Infectious Diseases, IRCCS San Raffaele Scientific Institute, Via Olgettina 58, 20132 Milan, Italy. Email: sitia.giovanni@hsr.it.

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Hepatocellular carcinoma (HCC), the primary cancer of the liver, is the fifth most common cancer and the second most common cause of cancer-related death worldwide with an expectancy to increase its incidence over the next 10–20 years (1). Although chronic viral infections [i.e., hepatitis B or C virus (HBV, HCV)], and chronic exposition to hepatotoxic factors such as toxins and alcohol are a major cause of HCC (2), in western countries and especially in the USA, obesity and dysregulated lipid metabolism are emerging as important non-viral factors associated with HCC (3,4). In particular, non-alcoholic fatty liver disease (NAFLD), a manifestation of the metabolic syndrome, is strongly associated with obesity and dyslipidemia (5,6). While most patients with NAFLD remain asymptomatic, about 20–25% progress to develop a more severe chronic hepatic inflammatory disease, defined as non-alcoholic steatohepatitis (NASH) a condition associated with liver fibrosis, cirrhosis and HCC (7,8).

Multiple evidences show that sedentary lifestyle, high-fat diet, obesity and inflammation-associated metabolic disorders such as insulin resistance and type 2 diabetes, can lead to increased intrahepatic secretion of free fatty acids (FFAs), adipokines and pro-inflammatory cytokines and the release of reactive oxygen species (ROS) that induces a chronic low-grade liver inflammatory condition that when unresolved promote hepatocellular death (5,9). In this pathogenic process, repetitive cycles of liver cell death and compensatory hepatocellular proliferation in the presence of mutagenic factors cause direct DNA damage and oncogenic mutations that favor neoplastic transformation and emergence of HCC (10) (*Figure 1*). Typically this phase of disease can last many years, also because the immune system has the ability to recognize and eliminate pre-tumor or tumor cells before they can cause overt disease in a process defined as tumor immune surveillance or elimination phase of the immune editing theory (11). According to this theory, transformed cells escaping intrinsic anti-tumor pathways are subjected to extrinsic anti-tumor mechanisms that detect and eliminate developing tumors before they become clinically manifest or establish an active equilibrium that control tumor expansion (12). Following these phases, either because of the emergence of tumor cells with reduced immunogenicity or by the engagement of numerous immune suppressor mechanisms involving different immune cell subsets, the anti-tumor immune functions that efficiently controlled nascent tumors, are attenuated thus contributing to HCC emergence and progression (12).

In this context, the study of Ma *et al.* describes a new functional link between high-fat diet, dysregulation of hepatic lipid metabolism and impaired liver anti-tumor immune surveillance (13). The authors, using different mouse models of NAFLD/NASH and human samples, show that dysregulation of lipid metabolism causes a selective loss of intrahepatic $CD4^+$ but not $CD8^+$ T lymphocytes, leading to accelerated hepatocarcinogenesis (13). In particular, high-fat diet induced intrahepatic accumulation

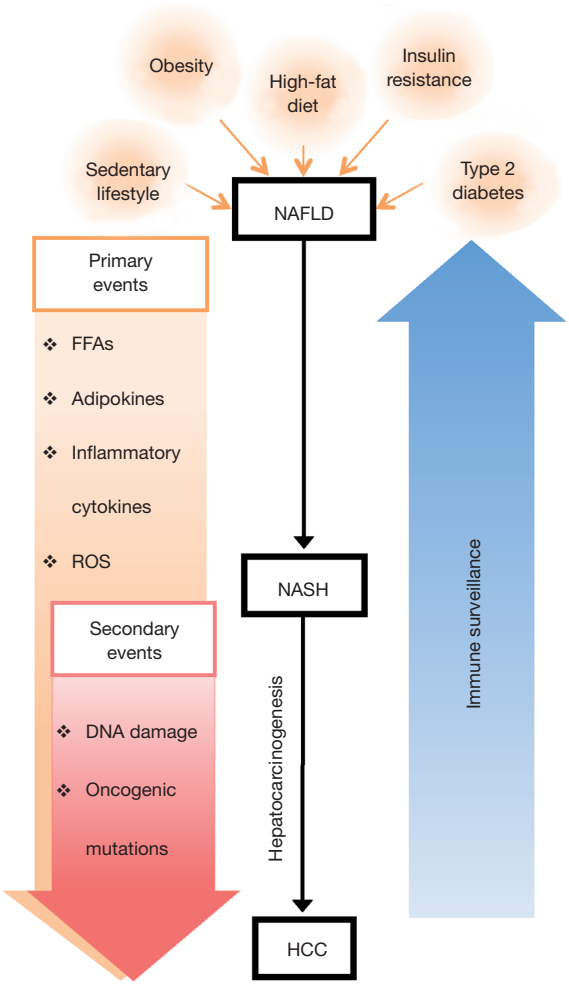

Figure 1 Hepatocarcinogenesis in non-alcoholic fatty liver disease (NAFLD). Sedentary lifestyle, obesity, high-fat diet and metabolic disorders like insulin resistance and type-2 diabetes, are factors that promote hepatosteatosis and NAFLD. Although majority of patients remain asymptomatic, about 20–25% proceed to a more severe condition in which steatosis is associated with inflammation, defined as non-alcoholic steatohepatitis (NASH). Thus, primary events such as the secretion of free fatty acids (FFAs), adipokines, pro-inflammatory cytokines and the release of reactive oxygen species (ROS) lead to chronic low-grade liver cell destruction. Accordingly, NAFLD/NASH, by inducing repetitive cycles of liver cell death and compensatory hepatocellular proliferation in the presence of mutagenic factors, promote secondary events like DNA damage and oncogenetic mutations that ultimately drive hepatocellular carcinoma (HCC) development and progression. These pro-tumoral processes are counterbalanced by the immune system that has the ability to eliminate mutated hepatocytes before they can cause overt disease, thus maintaining tissue homeostasis, in a process defined as tumor immune surveillance.

of linoleic acid (C18:2), but not other FFAs, seems to cause primarily the activation of hepatic $CD4^+$ T cells and the selection of α-fetoprotein (AFP)-specific $CD4^+$ T lymphocytes. Following this activation phase, as a consequence of extensive hepatic lipid accumulation, intrahepatic $CD4^+$ T lymphocytes die. The linoleic acid dependent intrahepatic $CD4^+$ T lymphocyte depletion, relies on the high mitochondrial mass and capacity of these cells to produce high levels of ROS, thus causing oxidative cellular damage, finally mediating their selective intrahepatic loss. Thus $CD4^+$ T lymphocytes, after an initial active immune surveillance towards AFP^+ tumor cells and probably also to other unknown tumor associated antigens, fail to control tumor progression due to their specific intrahepatic depletion. To further delineate the role of linoleic acid dependent ROS mediated of $CD4^+$ T lymphocyte death, the authors investigated the effect of ROS inhibitors such as catalase or N-acetylcysteine (NAC) on NAFLD-related HCC development. Importantly, catalase and NAC treatment significantly delayed NAFLD-promoted tumor development and this was associated with an effective maintenance of hepatic $CD4^+$ T lymphocytes, suggesting that prevention of intrahepatic $CD4^+$ T lymphocyte death mediates at least partially the anti-tumor effect of catalase and NAC therapy (*Figure 2*). Consistently with mouse data and with the finding that linoleic acid has also been identified as an important fatty acid in the context of NAFLD in humans, further support the idea that dysregulation of lipid metabolism and selective $CD4^+$ T lymphocyte intrahepatic depletion is part of the pathogenic process of NAFLD/NASH mediated hepatocarcinogenesis. Thus, hepatic $CD4^+$ T lymphocytes and their role in immune surveillance, together with NF-κB dysregulation, innate immune, inflammasome and Toll-like receptor activation represent important players in NAFLD/NASH pathogenesis (13-16), however, leaving open questions. First, the mouse model used does not allow to study lipid derived hepatic carcinogenesis in the context of liver cirrhosis, a conditions highly associated with NASH-mediated HCC development (17). Second, the pathogenic role of activated $CD4^+$ T lymphocytes in the inflammatory phase of NAFLD/NASH can't be excluded, and pharmacological interventions to restore immune surveillance has to be carefully taken into consideration because of the dual role of immune cells as mediators of liver damage and immune surveillance to tumor cells.

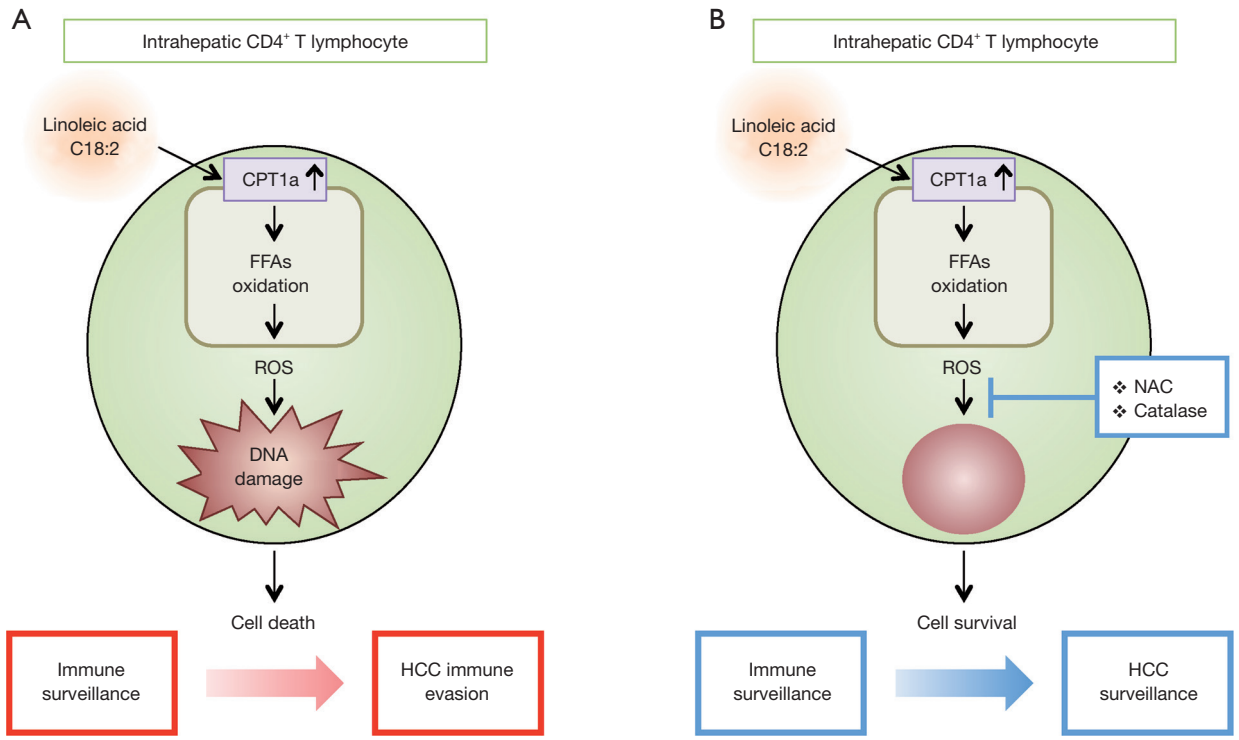

Figure 2 Linoleic acid-induced CD4+ T lymphocyte death impairs HCC immune surveillance. (A) Diet-induced intrahepatic accumulation of linoleic acid (C18:2), but not other FFAs, cause intrahepatic CD4+ T lymphocytes loss. This process is due to a specific up regulation of mitochondrial carnitine palmitoyltransferase 1a (CPT1a), the rate-limiting enzyme for importing FFAs into mitochondria, in CD4+ T lymphocytes with the increased production in these cells of reactive oxygen species (ROS) that in turn induce CD4+ T lymphocytes intrahepatic depletion. This specific loss of CD4+ T lymphocytes tilts the balance between an effective immune surveillance status to a phase of immune evasion of HCCs ultimately associated to progression from NAFLD/NASH to HCC; (B) blocking ROS within CD4+ T lymphocytes with N-acetylcysteine (NAC) or catalase spares hepatic CD4+ T lymphocytes depletion and restores immune surveillance thus preventing HCC progression. HCC, hepatocellular carcinoma; FFA, free fatty acid; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

Indeed, while metabolic activation of intrahepatic NKT and CD8+ T lymphocytes by lipids contribute to liver damage and promote NASH-driven hepatocarcinogenesis (18), other studies highlight that these same cells may also protect mice from acute-on-chronic liver injury (19), underlining the complex balance between different arms of the immune system. Finally, the definition of the long term consequences of intrahepatic CD4+ T lymphocyte loss in the broad context of microbial immunity to pathogens or microbiota, may be necessary to blow full light into the complex pathogenic mechanism implicated in NAFLD/NASH.

All in all, the results presented by Ma *et al.*, identify obesity-induced selective intrahepatic CD4+ T lymphocyte loss, as crucial new players in the pathogenesis of NAFLD/NASH induced carcinogenesis and suggest that the lack of CD4+ T lymphocyte-mediated immune surveillance plays a critical role in disease progression from NAFLD to HCC representing a new target for specific intervention.

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Footnote

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

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