Commentary

Comments on "NAFLD causes selective CD4+ T lymphocyte loss and promotes hepatocarcinogenesis"

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Non-alcoholic fatty liver disease (NAFLD) is increasingly diagnosed worldwide and is the most common cause of abnormal liver function tests and chronic liver disease in clinical practice. NAFLD includes non-alcoholic steatohepatitis (NASH) which is caused by cholesterol accumulation. NASH is characterized by an aberrant lipid storage in hepatocytes (1). Previous studies have proven that NASH can further progress to cirrhosis and hepatocellular carcinoma. And 10–15% with histologically proven NASH will progress to hepatocellular carcinoma (2). NAFLD related hepatic cellular cancer (HCC) is associated with shorter survival time and more advanced tumor stage (3). One of the most important molecular mechanisms of hepatocarcinogenesis is systemic immunosuppression.

Cholesterol contributes to innate immune suppression and chemotherapy resistance in hepatocellular carcinoma. Several studies have showed that innate immune play key role in the progress from NAFLD to cirrhosis and HCC (4,5). Cirrhosis and the early stages of HCC are characterized by chronic inflammation, but as the disease progressing local immune function is suppressed. The liver can be considered as an "immune organ", because it hosts non-lymphoid cells, such as macrophage Kupffer cells, stellate and dendritic cells, and lymphoid cells. Many of these cells are components of the classic innate immune system. Lipid accumulation trigger intracellular signaling pathways thus result in pro-inflammatory cytokines and activate innate immune system. An increasing number of studies have demonstrated that innate immune system regulate lipid metabolism through producing cytokines and other factors. It is well known that inflammation is risk factor of HCC (6,7). Many studies focused on proteomic and lipidomic signatures of lipid metabolism in NASH-associated hepatocellular carcinoma, and found the metabolisms are not the same to the normal liver cells (8). Immune evasions mediated by numerous immune suppressor mechanisms involving different immune cell subsets have been shown to contribute to HCC initiation and progression. De Minicis *et al.* (9) have found that dendritic cells link the innate and adaptive part of immune responses.

In an article published in the latest issue of *Nature*. Professor Ma *et al.* focused on the role of adaptive innate immune in the progression of HCC. And they also explored the regulation of lipid metabolism on innate immune in NAFLD. Results showed that the dysregulation of lipid metabolism in NAFLD causes a selective loss of intrahepatic CD4+ but not CD8+ T lymphocytes leading to accelerated hepatocarcinogenesis. They also found that CD4+ T lymphocytes have greater mitochondrial mass than CD8+ T lymphocytes and generate higher levels of mitochondrially-derived reactive oxygen species (ROS).

ROS causes damage to proteins, nucleic acids and contribute to carcinogenesis. A lot of studies have documented oxidative stress plays a vital role in both carcinogenesis and progression of HCC (10). ROS produced by cancer cells and tumor-infiltrating leukocytes

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can suppress the immune responses. ROS reduce T cell immune responses via inhibiting recognition between T cell receptor TCR and MHC-peptide complex (11). In the article, Ma *et al.* found that blockade of ROS reversed NAFLD-induced hepatic CD4+ T lymphocyte decrease and delayed NAFLD-promoted HCC. This article shed light on the regulation of ROS on innate immune reaction and provides new therapeutic method for treating HCC.

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Footnote

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

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