Editorial

Controlling cholesterol entry into mitochondria, a key step for hepatocarcinogenesis in non-alcoholic steatohepatitis-related hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second leading cause of cancer-related death worldwide (1). Unfortunately, the incidence and mortality of HCC are increasing steadily in formerly low-risk countries (2). Although the contribution of patients infected with hepatitis B virus (HBV) and hepatitis C virus (HCV) has dramatically decreased due to the use of highly effective antiviral agents, increasing epidemiologic evidence indicates a link between non-alcoholic fatty liver disease (NAFLD) and the risk of HCC (1). It is important to highlight that the prevalence of NAFLD has increased in parallel with the obesity, metabolic syndrome, and type 2 diabetes mellitus pandemic. Among patients with NAFLD, the incidence of HCC is around 0.44 per 1,000 person-years (3). The identification of the pathogenic mechanisms linking NAFLD and especially non-alcoholic steatohepatitis (NASH) to HCC is still a matter of study. Of particular importance in NASH-driven HCC is that a substantial proportion of patients have minimal or even no signs of liver fibrosis (4). In comparison with HCV, the risk of developing HCC is increased 5-fold in NAFLD and metabolic syndrome in non-cirrhotic patients (5).

Despite the advances in therapeutic strategies (immunostimulatory monoclonal antibodies, the PD-1 inhibitors atezolizumab and bevacizumab), the 5-years overall survival of patients with HCC in all stages is still poor, about 18% (1). Therefore, it is clear that new effective therapies are urgently needed for this devastating disease. Deeper insight into pathophysiology and mechanisms involved in hepatocarcinogenesis will definitively contribute to cover this gap. Still, the mechanisms of HCC development in NAFLD/NASH remain unclear and deserve profound investigation at the molecular level.

From the physiological point of view, synthesis of bile acids (BAs) in the liver is the major pathway for cholesterol output, and BAs are secreted into the bile to facilitate fat and vitamin digestion, but BAs also regulate metabolism, inflammatory responses, and gut microbiota. In addition, the association between HCC development and BAs metabolism has been demonstrated experimentally and in clinical settings (6-8).

BAs are synthesized from cholesterol in the liver through two main pathways, the classical/neutral and the alternative/acidic pathway. In the classical pathway, BAs are synthesized from cholesterol involving cholesterol-7-alpha-

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hydroxylase (CYP7A1), the initial and rate-determining step in this pathway of BA synthesis. Another important step is the conversion of 7α-hydroxy-4-cholestene-3-one by sterol 12α-hydroxylase (CYP8B1) to cholic acid (CA). In the alternative pathway, cholesterol is oxidized by mitochondrial sterol 27-hydroxylase (CYP27A1), located in the inner mitochondrial membrane (which contains very low cholesterol amounts), and its products are further hydroxylated by oxysterol 7α-hydroxylase (CYP7B1) with a subsequent enzymatic conversion to generate chenodesoxicolic acid (CDCA). The mitochondrial cholesterol level and therefore BAs metabolism is regulated by steroidogenic acute regulatory protein 1 (STARD1), but the alternative pathway of BAs synthesis has a minor contribution to the BAs pool (9).

The BAs homeostasis is regulated by the farnesoid X receptor (FXR) and G-protein coupled BA receptor 1 (GPBAR1/TGR5) (10). FXR plays a key role in regulating lipid metabolism and inflammation in the liver, and studies have shown that FXR expression is reduced in human HCC (11). Although we and others have shown that serum BA concentrations are elevated in advanced NASH, and that BAs accumulation induces liver damage and contributes to the progression of NAFLD, the role of the alternative BAs pathway in HCC development was not previously explored.

The work from Conde de la Rosa *et al.* elegantly demonstrated a key role for STARD1 in NASH-related HCC by the stimulation of mitochondrial BAs synthesis which further induced self-renewal and stemness in tumor-initiated stem-like cells (12). They first showed in patients with NASH-driven HCC an increased expression of STARD1 and BAs in liver tissue in comparison with controls. Then, they established a complex animal model, consisting of DEN-pretreated mice with a high-fat diet (HFD) supplemented with cholesterol to assess the effects on STARD1 expression and hepatocarcinogenesis; a more severe fibrosis degree was induced when compared to mice not supplemented with cholesterol, and the addition of cholesterol promoted NASH-related HCC and induced STARD1 expression. In addition, treatment with ezetimibe, an inhibitor of cholesterol absorption which previously showed anti-HCC effects (13), reduced tumor burden and increased animal survival, highlighting the role of cholesterol in the promotion of HCC development in the model studied.

In patients with NASH the presence of high levels of cholesterol and over-expression of STARD1 was previously reported by the authors (14), although, the role of STARD1 in hepatocarcinogenesis was not explored until now. The key role of STARD1 in HCC development was elegantly studied with knock-in and knock-down experiments in mice. Moreover, the effects of NASH-derived BAs profiles were investigated in tumor-initiated stem-like cells and primary mouse hepatocytes, where Conde de la Rosa *et al.* demonstrated that BAs stimulate the expression of transcription factors involved in self-renewal and pluripotency, which are key for HCC development (12).

Conde de la Rosa *et al.* provide a new mechanism of hepatocarcinogenesis in mice which involves the activation of the alternative BAs synthesis pathway (12). The authors could show a correlation between total BAs and the expression of STARD1 in humans and one might speculate that the activation of the alternative BAs synthesis pathway in metabolic syndrome, type 2 diabetes, obesity and NAFLD/NASH might be involved in the pathophysiology of HCC development. Therefore, is there any role for anticholesterol therapy for the chemoprevention of HCC development in NAFLD/NASH patients? In this regard, a recent systematic review and meta-analysis showed that use of statins was safe and associated with a lower pooled risk of HCC development among adults with chronic liver diseases (15).

In summary, controlling cholesterol entry into mitochondria might possibly inhibit a key step for hepatocarcinogenesis in NASH-related HCC.

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