


2017

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Liver Progenitor Cells and Cell Origin of Hepatocellular Carcinoma in Nonalcoholic Steatohepatitis

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ABSTRACT

The incidence of nonalcoholic fatty liver diseases (NAFLD) surpasses viral hepatitis and will be the main liver disorder in China in the next decades. Nonalcoholic steatohepatitis (NASH), as a progressive stage of NAFLD, may further progress to fibrosis and end-stage liver disease (ESLD). It is commonly known that liver cancer (majority in hepatocellular carcinoma, HCC) will occur in ESLD, however, it does happen in NASH without cirrhosis in a rate of 0.5-2.4%, which is very close to HCC in HCV infection. Therefore, it is intriguing to understand how NASH facilitates the fibrotic progression and HCC development, as well as the cell origins for HCC development in NASH. In addressing these questions, growing evidence demonstrates 1) Hepatic lipotoxicity and steatotic inflammation are the initiator for fibrogenesis by emphasizing the role of adipokines, cytokines and lymphokines as well as gut microbiota in the mediation of activation of Kupffer cells, hepatic stellate cells (HSCs) and sub-sets of lymphocytes; 2) Activation of inflammasome molecules elicits the activation of HSCs *in vitro* and *in vivo* and triggers a fibrogenic process; 3) Both repairing and regenerative responses to steatotic insults are the double-edge saws for tissue remodeling and could become the microenvironmental niche for HCC development; 4) Abnormal activation of pluripotent factors and hedgehog signaling molecules in liver progenitor cells is the driving force for malignant transformation from normal stem cells to cancer stem cells or tumor-initiating cells; and 5) JCAD acts as a novel regulator in the Hippo signal pathway and affects LATS2 phosphorylation activity by interacting with the kinase domain, promotes the formation and growth of xenografts. This gene is highly expressed in NASH-HCC patient specimens and a NASH-HCC model. Therefore, JCAD serves as a valued biomarker or molecular candidate for pharmacologic intervention in the development of NASH to HCC. Taken all together, the new insights into NASH fibrotic progression and cell origins of HCC development would aid in the discovery of innovative therapeutics for NASH treatment and establishment of prevention guidelines for HCC management.