Nonalcoholic fatty liver disease and hepatocellular carcinoma: Distinct links

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Although remarkable achievements have been made on the prevention and treatment of hepatocellular carcinoma (HCC), HCC remains a dreadful condition with high morbidity and mortality rates in patients with chronic hepatitis. The main risk factors of chronic hepatitis include hepatitis B virus (HBV), hepatitis C virus, alcohol, and nonalcoholic fatty liver disease (NAFLD), especially nonalcoholic steatohepatitis (NASH). NAFLD has been relatively unrecognized and underestimated in the past, which encompasses a broad spectrum of abnormalities, ranging from bland steatosis, steatohepatitis, and fibrosis to malignant transformation. The significance of NAFLD has gained much attention nowadays because of its high prevalence rate, association with obesity and metabolic syndrome, and the potential threats of liver cirrhosis and HCC. A recent meta-analysis enrolling 237 studies on Asian subjects has reported that the annual incidence of HCC was 1.8 cases per 1000 person-years in patients with NAFLD.[1] Although the incidence rate as compared to that in patients with chronic viral hepatitis is relatively low, the large number of patients with NAFLD has made it a nonnegligible risk factor of HCC. Furthermore, a global study has indicated that the incidence rate of HCC in patients with NASH reaches 5.29 per 1000 person-years,[2] which is remarkably higher. Although the annual cumulative incidence of HCC caused by NASH-related cirrhosis ranged from 0.46% to 2.6%,[3] previous studies have found that a significant portion of patients with NAFLD-related HCC were noncirrhotic, with the numbers being 46.2% in Italy, 37% in Switzerland, 34.6% in the United States, and 38.5% in Brazil.[4] Furthermore, a cross-sectional multicenter study in Japan revealed that almost 50% of histologically proven NASH cases developed noncirrhotic HCCs.[5] These findings raise an interesting concern, if NAFLD induces liver carcinogenesis via distinct pathways that bypass the course of liver cirrhosis, since most hepatitis B virus (HBV)-related HCCs develop under the background of cirrhotic livers.

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It is worth noting that molecular evidences from studies in human tumor tissue and animal models of NAFLD-induced HCC disclose that the NAFLD-related liver carcinogenesis is not only associated with significant changes in genetic background but also with changes in endocrine and metabolic pathways. First, comparative genomic hybridization (CGH) method detected that the genetic instability in patients with NASH is about 10- to 20-fold higher than in those with NAFLD. When NASH-specific variants were searched for alterations associated with HCC, two copy number variations located at 13q12.11 and 12q13.2 were identified, which harbor the exportin 4 (XPO4).[6] The XPO4 gene encodes a nuclear transporter and acts as a cargo protein between the cytoplasm and the nucleus.[7] Inactivation of XPO4-induced HCC in mice and XPO4 overexpression were linked to a better prognosis and increased survival in HCC patients.[8] Second, effector pathways that participate in the increased expression of cyclin D1, cyclin-dependent kinase 4 (Cdk4) and mouse double minute 2 (MDM2) in association with steatosis, and spontaneous HCC development are found in association with NAFLD and HCC development in the embryonic liver fodrin knock out mouse.[9] Stable or transient overexpression of platelet-derived growth factor C also resulted in hepatic steatosis and spontaneous HCC development, probably via receptor-mediated activation of PI3K and downstream signaling pathways.[10] Another animal model of steatosis and hepatic carcinogenesis is the fatty acyl-coenzyme A oxidase 1 (ACOX1) knockout mouse, where the lack of this specific peroxisomal enzyme that is required for degradation of very long chain fatty acid results in hepatic lipid accumulation, steatohepatitis, and HCC.[11] Third, a high fat diet-induced HCC animal model found that the link between steatosis and HCC development was inflammation, mediated by signaling via the lymphotoxin-β receptor (LTB).[12] Therefore, it is conceivable that liver carcinogenesis can be initiated in NAFLD without the prerequisite of liver cirrhosis.

Taken the aforementioned conditions into consideration and considering that the clinical features and outcomes of NAFLD-related HCC and hepatitis B-related HCC have not been compared in Asia populations, Lin et al[13] in the current issue of the *Journal of the Chinese Medical Association* published their findings: this study assessed and compared the clinical features and outcomes between patients with NAFLD- or HBV-related HCCs in Taiwan. Twenty-three NAFLD-related and 156 HBV-related HCC patients were enrolled. The authors found that NAFLD-related HCC patients were significantly older and heavier than those with HBV-related HCC. More of the NAFLD-related HCC patients were diabetic. 34.8% and 71.2% of patients with

NAFLD- and HBV-related HCC were cirrhotic, respectively, which was significantly different (p = 0.001). Tumor characteristics and overall survival were not significantly different between the two groups. It is well known that NAFLD is the hepatic presentation of metabolic syndrome, which links to obesity and diabetes closely. Consistently, a previous study discloses that HCC development is strongly affected by obesity in males.[14] In concordance with the current finding that more NAFLD-related HCC patients were diabetic, a Japanese study has therefore highlighted the importance of early HCC detection by ultrasound screening in diabetic patients.[15] In brief, the present study is the first one that demonstrates the significant ratio of noncirrhotic HCC in NAFLD patients and the contributing role of diabetes in Taiwan. These findings support a more aggressive, noninvasive cost-effective surveillance strategy for the early detection of noncirrhotic HCC in NAFLD patients that are older, obese, and diabetic.

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