Perspective

Novel susceptibility loci for hepatocellular carcinoma in chronic HBV carriers

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HBV is one of the most common causes of infectious liver disease. More than 400 million people are chronically infected with HBV in the world, and nearly 60% of liver cancers are related with HBV. However, clinical outcome after HBV exposure shows marked interindividual differences. Recent accumulated evidence indicates that host genetic factors play important roles in susceptibility and resistance to HBV infection. For example, genetic variations within HLA class II region were repeatedly shown to be associated with persistent HBV infection by candidate gene analyses and Genome wide association studies (GWAS) (1). In addition, the significant association of *KIF1B* with HBV-related hepatocellular carcinoma (HCC) in the Chinese population was reported (2). However the association between *KIFI1* and HBV-related HCC was not validated in other ethnic groups. Thus host factors related with hepatocellular carcinogenesis among patients with chronic HBV infection are still remained to be elucidated.

To identify genetic factors related with HBV-induced HCC, Li *et al*. conducted GWAS using 1,538 HBV-Positive HCC patients and 1,465 chronic HBV carrier (3). The top candidate SNPs were further analyzed in four independent cohorts totaling 4,431 HBV-positive HCC cases and 4,725 HBV carriers. They finally identified two novel associations at rs9272105 (HLA-DQA1/DRB1, OR=1.28 and P-value =5.24×10^{-22}) and rs455804 (*GRIK1*, OR=0.84 and P-value =5.24×10^{-10}). Recent GWAS identified the association of *MICA* and *DEPDC5* loci with HCV-induced HCC in the Japanese population. The authors also analyzed these loci in their sample set, however they found negative association of these loci, indicating that genetic factors associated with hepatocellular carcinogenesis are different between HCV and HBV.

SNP rs9272105 on 6p21.32 is located within MHC class II region. Since HLA-DQ and HLA-DRB1 alleles were previously reported to be associated with HCC risk, the authors further investigated the HLA alleles in their GWAS sample set. Concordant with the previous reports, they found the strong association of HLA-DRB1*0901 and DRBI*0405 with HBV-related HCC. However, SNP rs9272105 exhibited significant association even after adjustment with these HLA alleles. Thus, the association of rs9272105 identified by the authors did not simply reflect that of HLA alleles with HBV-related HCC.

SNP rs455804 on 21q21.3 is located within intron 1 of *GRIK1*. Since no other genes are included in this LD block, *GRIK1* is likely to be a susceptibility gene for HBV-related HCC. The *GRIK1* gene encodes CLUR5, one of the ionotropic glutamate receptor, which function as a subunit of ligand-activated channels and is involved in glutamate signaling. Glutamate has been shown to play a central role in the malignant phenotype of glioma through multiple molecular mechanisms. Inhibition of glutamate release and/or glutamate receptor activity can inhibit the proliferation and/or invasion of breast, laryngeal, and pancreatic cancer cells. In view of the previous observations, the association of *GRIK1* with HCC has elucidated the important role of glutamate signaling pathway in HBV-related HCC development.

However there are some limitations in this study. Firstly, the role of *GRIK1* in hepatocellular carcinogenesis is largely undetermined. Although other glutamate receptor family members and glutamate signaling are involved in human carcinogenesis, there are no functional evidence that GRIK1 is involved in hepatocellular carcinogenesis. In addition, the authors did not identify functional SNPs which affect the quality or quantity of GRIK1 protein. Therefore the association of GRIK1/glutamate pathway with HBV-induced HCC was still speculative. In addition,

HLA alleles were previously reported to be involved in HBV-induced HCC, the association of SNP in HLA class II region with HCC lacks novelty.

However these SNPs would be good prognostic markers for chronic hepatitis B (CHB) patients. Since most of the participants were not treated with interferon, risk estimation using these variations would be useful to determine therapeutic strategy for CHB patients. I hope that the association of these SNPs with HBV-related HCC would be evaluated in the other ethnic groups in the future.

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