The Role of Oncogenic Viruses in the Pathogenesis of Hepatocellular Carcinoma

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KEYWORDS

• Hepatocellular carcinoma (HCC) • Hepatitis B virus (HBV)
• Hepatitis C (HCV) • Cirrhosis

Hepatocarcinogenesis in humans is a multistep process, which reflects the genetic alterations that drive the progressive transformation of normal human cells into malignant cells.[1] Viruses may use diverse approaches that contribute to cancer development; however, additional factors such as host immunity and chronic inflammation, and host cellular mutations also play a role in the transformation process. More than 75% of all cases of hepatocellular carcinoma (HCC) are related to virus-induced hepatitis, mainly hepatitis B virus (HBV) and hepatitis C virus (HCV), leading to a 20-fold increased risk for the development of HCC in patients with chronic viral hepatitis.[2] Approximately 350 million people are chronically infected with HBV and 170 million with HCV worldwide; HBV infection is responsible for two-thirds of all HCC cases. The geographic distribution of HCC coincides with the distribution of HBV and HCV infections in those areas.[3]

A variety of viral and host factors contribute to HCC development in chronic HBV infection. Host factors include male gender, age older than 50 years, family history of HCC, and the presence of cirrhosis.[4] Other environmental and personal cofactors include excessive alcohol intake, cigarette smoking, obesity, and aflatoxin B1 (AFB1) exposure. The mycotoxin aflatoxin B1 (AFB1), produced by several fungal species of the *Aspergillus* genus, has strong hepatocarcinogenic potential and potentiates the carcinogenic effect of HBV infection.[5] That individuals infected with HBV who are exposed to aflatoxin have a higher risk of liver cancer than with either alone,

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suggests a synergistic effect between HBV and AFB1,[6] which has been reviewed comprehensively recently.[5] There is synergism between HBV and AFB1 in inducing oxidative stress and subsequently increasing the risk for HCC.[7] Wild and Montesano[5] suggested that HBV could predispose hepatocytes to carcinogenic activity based on the observation that cells expressing wild-type p53 transfected with HBx gene were more sensitive to the cytotoxic effects of AFB1 metabolites than were the parent cells.[8]

Among the viral factors that contribute to hepatocarcinogenesis are the level of HBV DNA in serum, hepatitis B e-antigen (HBeAg)-positive status, mutations in the viral genome, such as basal core promoter mutations (BCP T1762/A1764), genotype C, especially genotype C2 in Asia,[9,10] and genotype D.[11] Chronic infection with hepatitis virus D (HDV) is considered as a risk factor for HCC. However, a direct involvement of HDV in HCC development was not reported and it is believed that it might reflect the increasing severity of the disease in patient coinfected with HBV and HDV.[12] In addition, co-infection with other viruses such as HCV and HIV also increases the risk of HCC.[13]

HCV is a major cause of HCC worldwide owing to the high prevalence of HCV infection and the high rate of HCC occurrence in patients with HCV cirrhosis. In Japan, HCV is currently the main cause of HCC, accounting for more than 70% of cases. A similar rate is observed in Southern Europe, such as Italy or Spain. There are several risk factors for developing HCC in HCV-infected individuals, including cirrhosis and possibly even advanced hepatic fibrosis, heavy alcohol use, diabetes mellitus, obesity, low platelet count, male gender, older age, and increased hepatic iron stores.[14] A meta-analysis of 21 studies of age-adjusted risk showed that patients infected with HCV genotype 1b have an almost double risk for HCC development compared with other genotypes with a relative risk (RR) of 1.78.[15] Ishikawa and colleagues[16] showed, in a retrospective study of patients with positive HCV antibody, that male gender and a high titer of HCV-RNA were predictive factors for the development of HCC.

MECHANISM OF HEPATOCARCINOGENESIS

HCV-related HCC is generally agreed to occur on a background of cirrhosis and possibly severe fibrosis as well. Immune-mediated destruction of viral-infected hepatocytes induces liver regeneration that may lead to accumulation of mutations and subsequent selection of cells with a carcinogenic phenotype.[17–19] In HBV-related HCC, approximately 70% of cases occur in association with cirrhosis, which favors the hypothesis that HBV-related HCC may occur not only via cirrhosis.[20]

Both HBV and HCV viruses share many common features promoting cancer development. Although the mechanisms have not been completely clarified, they are believed to be different for each virus. The pattern of genetic alterations in viral-related HCC has been found to be quite discretely different for the 2 viruses. Gene expression, using microarray analysis, shows distinctively different patterns between HBV- and HCV-related HCC.[21] However, common pathogenetic pathways among the different etiological factors that induce HCC are suggested to contribute to the mechanisms of hepatocarcinogenesis, in particular, p53 inactivation or mutation and inflammation followed by continual rounds of necrosis and regeneration, and oxidative stress.[22]

Inflammation

The cross-talk between inflammatory cells and hepatocytes in the development of HCC is described in a detailed review published recently.[23] Emerging data suggest that the inflammatory milieu represents a favorable condition for genetic mutations.