Pathobiology of Human Hepatocellular Carcinoma

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The incidence of hepatocellular carcinoma has been increasing in Japan, and approximately 24,000 patients died of hepatocellular carcinoma in 1989. The incidence is 2.7 times higher in male than in female. Hepatocellular carcinoma is associated with hepatitis B virus infection in about 30% of cases, and with hepatitis C virus infection in the most of the remaining cases.

The incidence of hepatocellular carcinoma is high in Africa and East Asia, and that of hepatitis B virus infection is also high in these areas. Thus hepatitis B virus infection has been implicated in the genesis of hepatocellular carcinoma. Indeed it has been reported that hepatitis B virus genome is integrated in hepatocellular carcinoma tissues highly frequently¹⁻¹⁴. However integration of hepatitis B virus genome has been also reported to exist in non-cancerous hepatic tissue in patients with hepatitis B virus infection. In addition, the incidence of hepatocellular carcinoma in patients with asymptomatic hepatitis B virus infection is not high. These results lead to the conclusion that hepatitis B virus gene itself was not an oncogene. Although hepatitis B virus gene itself is not oncogenic, the X gene product has been reported to have trans-activator function^{15, 16} and may play some roles in hepatocarcinogenesis as a promoter. It has been reported that hepatitis B virus X-gene-transgenic mice develop hepatocellular carcinoma in a high frequency without any liver injury¹⁷ although hepatitis B virus X-gene itself is not considered as an oncogene.

In Japan, the incidence of hepatocellular carcinoma associated with hepatitis C virus infection is higher than that with hepatitis B virus infection. Recent progress has revealed that hepatitis C virus is an RNA virus with a positive-stranded genome comprising approximately 10,000 nucleotides¹⁸. It has been reported that hepatitis

C virus genome is not integrated in neither hepatocellular carcinoma tissues nor non-cancerous liver tissues. Hepatocellular carcinoma associated with hepatitis C virus infection is almost always associated with cirrhosis. These data suggest that chronic liver damage plays an important role in the human hepatocarcinogenesis.

Recently Chisari et al.¹⁹ has reported that hepatocellular carcinoma develops in hepatitis B virus-transgenic mice. They have clearly shown that integration of hepatitis B virus gene itself does not lead to development of hepatocellular carcinoma but chronic liver damage does. They showed that the deposition of large envelop protein of hepatitis B virus in hepatocytes of hepatitis B virus-transgenic mice lead to chronic liver injury followed by development of hyperplasia of the hepatocytes and eventually of hepatocellular carcinoma. Interestingly the incidence of hepatocellular carcinoma in hepatitis B virus-transgenic mice was higher in male mice than in female mice as observed in human hepatocellular carcinoma.

There have been increasing numbers of reports on the abnormalities of chromosomes²⁰⁻³⁰, and antioncogenes³¹⁻³⁵ in hepatocellular carcinoma, and they are implicated in the genesis of hepatocellular carcinoma. Chromosome abnormalities are considered to lead to either activation of oncogenes or loss of the function of antioncogenes. The abnormality of p53 antioncogene was first reported in hepatocellular carcinoma cell lines^{31, 32}. The p53 abnormality was also observed highly frequently in hepatocellular carcinoma from Africa and China, and it was shown to be due to the point mutation at codon 249^{33, 34}. However, Hosono³² has reported that the p53 abnormality is a rare event in hepatocellular carcinoma. Murakami³⁵ has reported that they could not detect the abnormality of p53 gene in any of 21 early hepatocellular carcinoma in Japan and that they could detect the abnormality in only 8 out of 21 advanced

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hepatocellular carcinoma in Japan. In addition, point mutation of p53 gene was not restricted to codon 249, and the abnormalities of RB gene have been reported to be observed in hepatocellular carcinoma with p53 gene abnormalities. Since codon 249 of p53 gene is the site of point mutation caused by aflatoxin B₁, the results suggest the implication of aflatoxin in hepatocarcinogenesis in Africa and China.

Androgen receptor has been demonstrated to exist in both hepatocellular carcinoma and non-cancerous liver tissues³⁶. When cloned androgen receptor-positive human hepatocellular carcinoma cells were inoculated in male and female nude mice, the incidence of successful implantation of the cells was much higher in male mice than in female mice (unpublished data). The incidence of successful implantation on the cells in female nude mice was increased to that in male mice by supplement with androgenic hormone. Thus androgenic hormone is supposed to affect the growth of hepatocellular carcinoma cells through androgen receptor.

To take the reported results together, we can postulate the mechanisms of hepatocarcinogenesis in human as shown in Fig.1. Chronic liver damage of any etiology leads to liver cell necrosis and regeneration. During liver regeneration, liver cells proliferate and are susceptible to mutagenic agents (environmental factors, hepatitis virus, cytokines and free radicals generated by inflammation, etc.). The growth of transformed hepatocytes may be accelerated by androgenic hormones, hepatitis virus products, and other factors, leading to the genesis of hepatocellular carcinoma.

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