Hepatitis C Virus and Hepatocarcinogenesis

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Among the clinical manifestations associated with chronic hepatitis C virus (HCV) infection, which include both hepatic and extrahepatic ones, hepatocellular carcinoma (HCC) is the most important, because HCC associated with HCV has one of the highest mortality rates in the world. Despite the overwhelming evidence from clinical studies linking chronic HCV infection to the development of HCC, the precise role of HCV in hepatocarcinogenesis remains unclear. It is postulated that HCV may promote the development of HCC by inducing continuous cell death followed by regeneration, whereby genetic damage accumulates to confer growth advantage on the hepatocytes. In this scenario, HCV has only an indirect association with hepatocarcinogenesis. Another possibility is the direct involvement of HCV in hepatocarcinogenesis, wherein the product(s) of the virus may be involved in regulating cell proliferation.

The HCV core protein is an unglycosylated protein of about 22 kDa. It has recently been shown that the core protein accumulates, in part, into the nuclei even when the core gene cDNA is expressed in its native form, i.e., without artificial cleavage of its C-terminal portion. This implies that the core protein may have a direct effect on the pathogenesis of diseases caused by HCV.

We have derived three transgenic mouse lineages having the HCV core gene. These transgenic mouse lines had the HCV core gene of genotype 1b under the control of hepatitis B viral regulatory elements, which have been shown to allow high-level expression of genes in transgenic mice without interfering with mouse development. Founder mice were back-crossed to C57BL/6. Southern blotting of genomic DNA revealed a distinct integration pattern for each lineage. Mice of F1 to F3 generation from the lineages C21 and C49, not homozygous but heterozygous for the transgene, were investigated, to avoid the possibility that a certain genetic background trait is converged by the continual brother-sister mating of mice.

In both lineages, the expression of the core protein in the liver started at birth and continued for at least 23 months thereafter. Most importantly, the intrahepatic levels of the core protein were almost comparable to
those in the liver tissues from patients with chronic hepatitis C. This finding indicated the appropriateness of these transgenic models for study of the liver disease spectrum in human HCV infection. These transgenic mice develop hepatic steatosis, which is one of the characteristic histopathological features of chronic hepatitis C, at as early an age as 3 months. Steatosis, which is characterized by hepatocytes with fat droplets of various sizes in the cytoplasm, continued to progress slowly up to the age of 12 months. However, no inflammation was observed in the liver during that period.

Hepatic tumors began to develop in the liver of transgenic mice from the age of 16 months. Microscopic examination revealed hepatic nodules which compressed the neighboring non-tumorous liver parenchyma and were made up of eosinophilic cells with fat droplets in the cytoplasm. Some of the hepatic nodules developed as well-differentiated HCC with trabecular features, with the cells containing fat droplets in the cytoplasm. Interestingly, most of the hepatic tumors exhibited a remarkable "nodule in nodule" characteristic, wherein HCC developed in the midst of an adenoma or a better-differentiated HCC. A cluster of carcinoma cells appeared in the center of adenoma cells compressing the neighboring normal hepatocytes. It should be noted that the fat droplets in the cytoplasm of the cells composing the hepatocellular adenoma were as numerous as those in the non-tumorous parts, whereas cells composing HCC had much fewer fat droplets. This feature closely resembles that observed in association with the development of HCC in human chronic hepatitis C; small well-differentiated HCCs or their precursors occasionally show marked fatty changes, whereas more poorly-differentiated HCCs developing from within them show little fatty changes.

These results indicate that the HCV core protein has a major role in the development of HCC and that HCV itself is directly involved in hepatocarcinogenesis. The presence of the HCV core protein, which has an oncogenic potential, may allow some of the steps in multistep hepatocarcinogenesis to be skipped. This may explain the very high frequency of HCC in cases with HCV infection.
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Viral Hepatitis, Hepatocarcinogenesis, General Viral Infection.

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