atitis B surface antigen-negative individuals. The clinical relevance of this peculiar infection, in particular, the impact of occult HBV infection in cases of HCC has been a matter of debate. Prevalence and molecular status of occult HBV in patients with HCC has been investigated in several studies. HCC patients from Italy, France, Japan, Morocco, the United States, Canada etc.....who had no detectable HBsAg in their serum have been studied. In these HBsAg-negative HCC patients, HBV DNA was detected in tumorous and/or in adjacent non tumorous liver tissue using polymerase chain reaction (PCR) in almost half of the patients, being anti-HCV positive or not. Some of the patients are positive for anti-HBc antibodies as the only marker of HBV infection, but not all. Covalently closed circular HBV DNA may be detected indicating that at least some of these patients had actively replicating HBV infections. Observational cohort study showed that, among the HBsAg-negative patients with chronic hepatitis C, HCC develops for the most part in carriers of occult HBV.

One of the markers in HCC cases, HBsAg (-), has been the presence of the HBV-X gene expression in HCC since positivity for the HBV-X protein in liver tissue in several studies reached half of the liver tissues specimens. In all studies, the significant association of occult HBV with HCC was irrespective of age, sex, and may be contemporary with hepatitis C virus infection. Both integrated viral DNA and covalently closed circular HBV genomes were detected in patients with occult HBV. Moreover, the presence of free HBV genomes was associated with persistence of viral transcription and replication: There are evidences that occult HBV is a risk factor for the development of HCC and that the potential mechanisms whereby overt HBV might induce tumour formation are mostly maintained in cases of occult infection

HCV and HCC molecular epidemiology

FLOR H. PUJOL[1]

iHepatitis C virus (HCV) is a member of the family Flaviviridae, responsible for the majority of the non-A non-B post-transfusion hepatitis before 1990. Around 170 millions persons in the world are thought to be infected with this virus. A high number of HCV-infected people develop cirrhosis and from these, a significant proportion progresses to hepatocellular carcinoma (HCC). Six HCV genotypes and a large number of subtypes in each genotype have been described. Infections with HCV genotype 1 are associated with the lowest therapeutic success. HCV genotypes 1, 2, and 3 have a worldwide distribution. HCV subtypes 1a and 1b are the most common genotypes in the United States and are also are predominant in Europe, while in Japan, subtype 1b is predominant. Although HCV subtypes 2a and 2b are relatively common in America, Europe, and Japan, subtype 2c is found commonly in northern Italy. HCV genotype 3a is frequent in intravenous drug abusers in Europe and the United States. HCV genotype 4 appears to be prevalent in Africa and the Middle East, and genotypes 5 and 6 seem to be confined to South Africa and Asia, respectively.

HCC accounts for approximately 6% of all human cancers. Around 500,000 to 1 million cases occur annually worldwide, with HCC being the fifth common malignancy in men and the ninth in women. HCC is frequently a consequence of infection by HBV and HCV.

1. Director Molecular Virology Lab. CMBC, Instituto Venezolano de Investigaciones Científicas, Caracas, Venezuela. fpujol@ivic.ve

The first line of evidences comes from epidemiologic studies. While HBV is the most frequent cause of HCC in many countries of Asia and South America, both HBV and HCV are found at similar frequencies, and eventually HCV at a higher frequency than HBV, among HCC patients in Europe, North America, and Japan. The cumulative appearance rate of HCC might be higher for HCV-infected cirrhotic patients than for HBV-infected ones.

HCV genotype 1b has also been more frequently associated with a more severe liver disease. However, this association seems to be due to the fact that individuals infected with this genotype have a longer mean duration of infection. An heterogeneity in the IFN sensitivity determining region (ISDR) of HCV genotype 1b isolates has been observed in patients presenting with HCC, compared with the isolates of patients presenting with liver cirrhosis without HCC, which exhibit a more homogeneous ISDR region, although an opposite observation has been reported by others. Some nucleotides in the 5' non-coding region and specific amino acid substitutions within the entire HCV genome have been also found in the HCV strains infecting patients with HCC. Hepatic steatosis is a common consequence of HCV infection, particularly HCV genotype 3, and has been recently associated with the development of HCC. Steatosis might be contributing to the progression of fibrosis in HCV-related disease. More studies are needed to evaluate an eventual correlation between HCV genotype 3, the presence of steatosis, and progression to HCC.

Even if it seems that an effective vaccine against HCV will not be readily obtained in the near future, available therapeutic approaches seem to delay the progression to HCC in infected patients who respond at least transiently to treatment. The evolution to HCC associated with infection by HCV seems to be a multifactor process. Although the role of chronic infection with HCV in the etiology of liver cancer is well established, more studies are needed to assess the individual contribution of specific viral strains in the development of HCC. The limited arsenal available against HCV (improving therapeutic agents) is crucial since it might prevent or delay the development of HCC.

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Molecular basis of hepatitis C virus -associated hepatocarcinogenesis

ISABELLE CHEMIN[1]

In areas with an intermediate rate of Hepatocellular Carcinoma (HCC) such as Western Europe and Japan, hepatitis C is the predominant cause, whereas in low rate areas such as Western Europe and North USA, HCC is often related to other factors as alcoholic liver disease. There is a rising incidence in HCC in developed countries during the last two decades, due to the increasing rate of hepatitis C infection and improvement of the clinical management of cirrhosis (most of the time appear after cirrhosis), the total number of

1. Scientist CR1, INSERM U271, Lyon, France. chemin@lyon.inserm.fr