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

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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

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HCC cases annually registered should be multiplied by 3 until 2020.

The pathogenesis of HCC in HCV infection has extensively been analysed. Hepatitis C virus-induced chronic inflammation and the effects of cytokines in the development of fibrosis and liver cell proliferation are considered as one of the major pathogenic mechanisms. Increasing experimental evidence suggests that HCV contributes to HCC by directly modulating pathways that promote the malignant transformation of hepatocytes. Hepatitis C virus is an RNA virus that does not integrate into the host genome but HCV proteins interact with many host-cell factors well beyond their roles in the viral life cycle and are involved in a wide range of activities at least in vitro, including cell signalling, transcription, cell proliferation, apoptosis, membrane rearrangements, vesicular trafficking and translational regulation. At least four of the HCV gene products, namely HCV core, NS3, NS4B and NS5A, have been shown to exhibit transformation potential in tissue culture and several potentially oncogenic pathways have been shown to be altered by the expression of HCV proteins. Both HCV core and NS5A induce the accumulation of wild-type beta-catenin and the Wnt-beta-catenin pathway emerges as a common target for HCV (and HBV) in human HCCs, also independently from axin/beta-catenin gene mutations. Induction of both endoplasmic reticulum stress and oxidative stress by HCV proteins might also contribute to HCV transformation. HCV proteins were shown to have an action on tumor suppressor genes, mitosis, apoptosis. Most of the putative transforming functions of the HCV proteins have been defined in artificial cellular systems, which may not be applicable to HCV infection in vivo, and still need to be established in relevant infection and disease models.

Despite numerous lines of epidemiologic evidence connecting HCV infection and the development of HCC, it remains controversial whether HCV itself plays a direct role or an indirect role in the pathogenesis of HCC. Through the use of transgenic mice, it has become evident that the core protein of HCV has oncogenic potential. HCV is directly involved in hepatocarcinogenesis, albeit other factors such as inflammation and environmental factors might also play a role. The direct involvement of HCV in hepatocarcinogenesis would be achieved via at least 2 pathways. In one pathway, the core protein acts on the function of mitochondria, leading to the overproduction of oxidative stress, which yields genetic aberrations in cell growth-related genes. The other pathway involves the modulation of cellular gene expressions and intracellular signal transductions, such as mitogen-activated protein kinase pathway, which results in the activation of transcription factors and cell cycle machineries. The combination of these alterations would provoke the development of HCC in HCV infection. This may be a mechanism for HCC development in HCV infection that is distinct from those for other cancers. The presence of the HCV core protein, to which an oncogenic potential is ascribed, might allow some of the multiple steps to be bypassed in hepatocarcinogenesis. Therefore, unlike in other cancers, HCV infection might elicit HCC in the absence of a complete set of genetic aberrations since it mainly develop in a context of wild type P53 status and absence of genetic instability. Such a scenario, may explain the unusually high incidence and multicentric nature of HCC development in HCV infection.

HBV And HCV Molecular Evolution

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Hepatitis B virus (HBV) infection is still a significant health concern in in the world, since around 2 billion persons have been infected by this virus (HBV) and around 350 millions of them are chronic carriers, in spite of a highly effective vaccine against this virus. Bearing a reverse transcriptase necessary for its rep-

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