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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lication but with a highly compacted genome, this hepadnavirus exhibits a degree of variability intermediate between DNA and RNA viruses. This plasticiy leads to the generation of several mutants and genotypic variability. HBV mutants develop during the natural course of infection and play an important role in the evasion of the selective pressure applied by the host (immune or chemotherapeutic).

Eight HBV genotypes (A-H) have been described, based on a minimum divergence of 8% of the complete genome sequences. HBV genotype F is the most divergent of the HBV genotypes, is autochthonous to South America and is highly predominant in the Northen region of South America. The recently described HBV genotype H is closely related to genotype F and seems to be restricted to Central and North America. Recombination among different HBV strains seems to be frequent. Several subgenotypes have also been described inside HBV genotypes, which exhibit a geographic pattern of distribution. The clinical and biologic importance of the genotypic diversity of HBV is of major concern at the present moment and has been studied in Asia and Europe. The origin of HBV is still an open question. Depending on the model used for the phylogenetic analysis, an Asian or an American origin of HBV has been proposed. By revisiting the genotypic diversity of HBV, an alternative explanation is that human HBV genotypes might have emerged by several zoonotic introductions, both in the Old and the New World..

Around 170 millions persons in the world are thought to be infected with hepatitis C virus (HCV). Six genotypes and a large number of subtypes in each genotype have been described for this member of the Flaviviridae family. Infections with HCV genotype 1 are associated with the lowest therapeutic success. 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. HCV genotypes 1, 2, and 3 have a worldwide distribution and display an apidemic pattern of 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 theMiddle East, and genotypes 5 and 6 seem to be confined to South Africa and Asia, respectively. These last genotypes display an endemic pattern of distribution. In addition, a change in the frequency of the prevailing genotypes has been described in several countries: in general, HCV genotype 1b is being displaced by genotypes 3a and/or 2. Coalescent studies have allowed to describe the epidemic pattern of dissemination of some HCV subtypes in specific countries, generally around 100 years ago. The origin of this virus is still an open question, but several studies traces it diversification only around 1,000 years ago.

The replication of HCV is dependent on a RNA-polymerase RNA dependent which lacks proofreading activity, which confers to this virus a high rate of variability. This virus circulates as a quasispecies. This population dynamic inside a single strain confers to this virus the ability to support and evade several selective pressures imposed by the host, like the innate immune response, the production of neutralizing antibodies and cytotoxic lymphocites. More recently, even if many drugs currently developed against HCV have not been aproved yet for use in humans, in vitro studies have allowed to identified already drug resistance mutations. As for HIV, these mutation may be resulting also in a reduction of viral fitness, and compensatory mutations have also been described, that restore at least partially the replication capacity of the mutated viruses. The extensive variability of HCV is one of the main reasons that had hampered the production of an eefective vaccine against this virus.

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