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Viral hepatocarcinogenesis

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Hepatocellular carcinoma (HCC; also known as malignant hepatoma) kills approximately 500,000 persons throughout the world each year, with 80-90% of HCC-related deaths occurring in Asia. HCC is highly aggressive clinically, and is the 5th leading cause of cancer-related death globally. Chronic infections with either hepatitis B virus (HBV), or hepatitis C virus (HCV), increase the relative risk of liver cancer by 20-200%; these chronic viral infections are present in over 70% of HCC cases, and iatrogenic interventions against these viruses significantly reduce the risk of liver cancer development. Thus, clinical evidence implicates chronic viral hepatitis as a potent cofactor in liver cancer development, if not a direct cause. The Woodchuck Hepatitis Virus (WHV)-induced hepatocarcinogenesis model provides additional strong evidence for a direct viral role in liver cancer, since 100% of animals infected with WHV develop liver cancer. Importantly, WHV is a close relative of HBV, with a similar viral lifecycle. However, viral-induced liver cancer models are lacking for both HBV and HCV infection, so causal relationships and mechanisms operating during viral hepatocarcinogenesis remain unproven. None-the-less, molecular studies have provided important insights into viral-host interactions, operating during the HBV and HCV life cycles, which potentially play critical roles in carcinogenesis. Well beyond the assumption that liver cancer is an indirect result of necro-inflammation, molecular studies have demonstrated broad and potentially deleterious direct effects of viral protein expression on numerous key host regulatory processes, including cell cycle control, cell differentiation, cell signaling, apoptosis, and DNA repair. As additional mechanisms, HBV, a DNA virus, is capable of integration into host genomes and disrupting cell gene expression, while HCV, an RNA virus, exerts profound effects on mitochondrial function, hepatic free radical metabolism, and innate immunity. Finally, transgenic mouse models have implicated specific HBV and HCV gene products as cell transformation inducers. In summary, HCC is a major killer of humans, and studies of viral-induced tumor cell biology have indicted that HCC development is a multi-step process, very likely facilitated by cell dysregulatory properties of hepatitis B or C viral gene products.