lecular mechanisms driving HBV-associated carcinogenesis, and thus potentially identify new strategies in diagnosis and therapy.

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Cell cycle deregulation by the HBx protein of hepatitis B virus

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Cell cycle control by oncogenic viruses usually involves disruption of the normal restraints on cellular proliferation via abnormal proteolytic degradation and malignant transformation of cells. The cell cycle regulatory molecules viz. cyclins, cyclin-dependent kinases (cdks) and inhibitors of cdks as well as the transcriptional targets of signaling pathways induce cells to move through the cell cycle checkpoints. These check points are often found deregulated in tumor cells and in the cells afflicted with DNA tumor viruses predisposing them towards transformation. The X protein or HBx of hepatitis B virus is a promiscuous transactivator that has been implicated in the development of hepatocellular carcinoma in humans. However, the exact role of HBx in establishing a permissive environment for hepatocarcinogenesis is not fully understood. HBx activates the Ras-Raf-MAP kinase signaling cascade, through which it activates transcription factors AP-1 and NF-kappa B, and stimulates cell DNA synthesis.

HBx shows a profound effect on cell cycle progression even in the absence of serum. It can override the replicative senescence of cells in G0 phase by binding to p55sen. It stimulates the G0 cells to transit through G1 phase by activating Src kinases and the cyclin A-cyclin-dependent kinase 2 complexes, that in turn induces the cyclin A promoter. There is an early and sustained level of cyclin-cdk2 complex in the presence of HBx during the cell cycle which is coupled with an increased protein kinase activity of cdk2 suggesting an early appearance of S phase. The interaction between cyclin-cdk2 complex and HBx occurs through its carboxy-terminal region (amino acids 85-119) and requires a constitutive Src kinase activity. The increased cdk2 activity is associated with stabilization of cyclin E as well as proteasomal degradation of cdk inhibitor p27Kip1. Notably, the HBx mutant that fails to interact with cyclin-cdk2 complex, also fails to destabilize p27Kip1 or deregulate cell cycle. Thus, HBx appears to override normal cell cycle restraints by directly interacting with the key cell cycle regulators and modu-

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lating their activities. These data suggest a molecular mechanism by which HBx likely contributes to viral carcinogenesis. Driving the HBV-infected cells to grow continuously may be essential for active viral replication that could facilitate the full manifestation of the oncogenic potential of HBx.

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Hepatitis infections, aflatoxin and hepatocellular carcinoma

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The incidence rates of hepatocellular carcinoma (HCC) show large geographic variations, globally reflecting the prevalence of two main aetiologic factors, hepatitis B (HBV) and/or C (HCV) virus infection and exposure to high levels of aflatoxin in the diet (Chen et al. 1997). The highest incidence rates are observed in regions where most of the population is exposed to both factors, such as in parts of eastern Asia and in sub-Saharan Africa (Parkin et al. 2001). These high incidences are consistent with the fact that HBV chronicity and exposure to aflatoxin have a multiplicative effect of risk for HCC. Depending on aetiology and geographic area, mutations in TP53 show striking differences in prevalence and pattern. In Europe and the US, where alcohol is a major risk factor in addition to viral infections, mutations occur in about 25% of HCC and show as much diversity in their type and codon position as in most other epithelial cancers. However, in high incidence areas such as Mozambique, Senegal, The Gambia (Africa) and Qidong county (China), TP53 is mutated in over 50% of the cases and the vast majority of these mutations are a single missense, hotspot mutation at codon 249, AGG to AGT, resulting in the substitution of arginine into serine (249ser). This mutation is uncommon in regions where aflatoxin is not present at significant levels in the diet. In areas of intermediate exposure to aflatoxin, as for example in Thailand, the prevalence of the 249ser mutation is intermediate between high- and low-incidence areas. Thus, there is a dose-dependent relationship between exposure to aflatoxin, incidence of HCC and prevalence of 249ser mutation. Aflatoxins are toxic and carcinogenic metabolites produced by several varieties of molds, mainly Aspergillus flavus and Aspergillus parasiticum. These molds contaminate a wide range of traditional agricultural products in countries with hot, humid climates, including maize, peanuts and cottonseeds. The toxins are present at significant levels in crops at the time of harvest but their concentration further increases under poor conditions of long-

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