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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term food storage, in particular during the rain season. Thus, in these regions, most inhabitants of rural areas are highly exposed to aflatoxins, with seasonal variations reflecting the consumption of stored versus fresh foodstuff. Population-based surveys have demonstrated the presence of serum aflatoxin-albumin adducts in over 95% of the normal population in The Gambia, West Africa. Exposure starts in the perinatal period, through in utero transfer and breast-feeding, and continues throughout life, mainly from consumption of peanuts. Time patterns of aflatoxin-albumin adduct levels correlate with the seasonal availability of peanuts.

There is strong experimental evidence that aflatoxins are potent hepatocarcinogens in rodents. In humans, there are good ecological correlations between the risk of HCC and the presence of biomarkers of aflatoxin exposure in serum or in urine .The most significant carcinogenic aflatoxin is B1 (AFB1), which is the most abundant in the diet. AFB1 is metabolized in the liver by several CYP450 enzymes (mainly 1A2 and 3A4) to a reactive AFB1-8,9-exo-epoxide (Mace et al. 1997). This metabolite generates a primary DNA adduct (8-9, dihydro-8-(N7-guanyl)-9-hydroxyaflatoxin; AFB1-N7-Gua), naturally converted to two secondary lesions, an apurinic (AP) site and a stable, AFB1-formamidopyrimidine (AFB1-FAPY) adduct The latter is considered as the most mutagenic lesion (Smela et al. 2002). The sequence context of codon 249 (AGGCC) represents a site of intermediate affinity for the formation of AFB1-induced lesions. Other codons in TP53, including some codons that are "hotspots" in many cancers (codon 245, 248 and 273), have a similar or even greater affinity for AFB1 than codon 249. Thus, the selectivity for 249ser in HCC cannot be solely explained by thepreferential formation of adducts at this position and other factors must play a role to select this particular mutation as the major carcinogenic one in liver cells exposed to aflatoxins.

There is evidence that imperfect DNA repair may increase the risk of mutagenesis and carcinogenesis induced by AFB1. Higher levels of AFB1-DNA adducts have been detected in the placenta of healthy women from Tawain carrying the Gln399 allele of XRCC1, an enzyme involved in base excision repair, causing slower repair and persistence of DNA adducts. Together, these results suggests that deficient DNA repair does not explain the high prevalence of 249ser in HCC, and that biological selection may play a role to facilitate the clonal expansion of cells carrying 249ser during the development of HCC.

Occult HBV infection and HCC

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A number of risk factors appear to play a role in Hepatocellularcinoma (HCC), HBV infection being one of the most important. Chronic inflammation and cytokines are key determinants in the development of fibrosis and liver cell proliferation. HBV DNA integration into host cellular DNA, has been extensively studied and may disrupt or promote expression of cellular genes that are important in cell growth and differentiation. Moreover, expression of HBV proteins may have a direct effect on cellular functions, and some of these gene products may lead to malignant transformation. Several HBV genes have been frequently found in infected tissues including truncated pre-S2/S, hepatitis B X gene, and a novel spliced transcript of HBV (hepatitis B spliced protein). The proteins expressed from these integrated genes have been shown to have intracellular activities, including effects on cellular growth and apoptosis.

Occult hepatitis B virus (HBV) infection is characterized by persistence of HBV DNA into the tissue of hep-

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