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Hepatitis B virus DNA integration and transactivation of cellular genes

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Chronic hepatitis B virus (HBV) infection is etiologically related to human hepatocellular carcinoma (HCC). Most HCCs contain integrated HBV DNA in hepatocyte, suggesting that the integration may be involved in carcinogenesis. Available data on the integrants from human hepatocellular carcinomas seem to represent primary integrants as well as the products of secondary rearrangements. By means of structural analyses of the possible primary integrants, it has been observed that the replication intermediates of the viral genome are the preferred substrates for integration. The integrated HBV DNA and the target cellular DNA are invariably associated with deletions, possibly reflecting the substrate for, and the mechanism of, the integration reaction. The host DNA sequences as well as the target site of integration in chromosomes are selected randomly suggesting that HBV DNA integration should bring about random mutagenic effects. Analysis of the samples recovered from hepatocellular carcinomas show that the integrated HBV DNA can mediate secondary rearrangements of chromosomes, such as translocations, inversions, deletions and (possibly) amplifications. The integration of HBV DNA into the host genome occurs at early steps of clonal tumor expansion. The integration has been shown in a number of cases to affect a variety of cancer-related genes and to exert insertional mutagenesis. However, in contrast to the woodchuck model, in which specific HBV-DNA integration is detectable in most cases, insertional activation or inactivation of cellular genes appears to be a rare event in man. The discovery of transactivating functions exerted by HBx and truncated HBs(urface) proteins supports the notion that these could be relevant to hepatocarcinogenesis as these transactivator sequences have been found in a large number of HCC tumors or hepatoma-derived cell lines. The HBx transactivator can stimulate a wide range of cellular genes and displays oncogenic potential in cell culture as well as in a transgenic environment. The HBs transactivators are encoded by the preS/S region of S gene and may involve carboxy terminal truncation to gain transactivation function. Expression of host genes by viral transactivators is mediated by regulatory elements of the cellular transcription factors like c-fos, c-myc, NF-kappa B, SRE and Sp1. Thus, during hepatitis B infection, the tendency of rearrangement of hepatocyte chromosomes is combined with the forcible turnover of cells. This is a constantly operating system for the selection of cells that grow better than normal cells, possibly involving important steps in multi-staged hepatocarcinogeneses. Gene expression profiling and proteomic techniques may help to characterize the mo-

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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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