Hepatitis B virus promotes β-catenin-signalling and disassembly of adherens junctions in a Src kinase dependent fashion.

Hepatitis B virus (HBV) infection is a prominent cause of hepatocellular carcinoma (HCC) but the underlying molecular mechanisms are complex and multiple pathways have been proposed such as the activation of the Wnt-β-catenin-signalling and dysregulation of E-cadherin/β-catenin adherens junctions. This study aimed to identify mechanisms of how HBV infection and replication as well as HBV X protein (HBx) gene expression in the context of an HBV genome influence Wnt-β-catenin-signalling and formation of adherens junctions and to which extent HBx contributes to this. Regulation of E-cadherin/β-catenin junctions and β-catenin-signalling as well as the role of HBx were investigated using constructs transiently or stably inducing replication of HBV+/−HBx in hepatoma cell lines. In addition, HCC and adjacent non-tumorous tissue samples from HBV-infected HCC patients and drug interference in HBV-infected cells were studied. Although HBV did not alter overall expression levels of E-cadherin or β-catenin, it diminished their cell surface localization resulting in nuclear translocation of β-catenin and activation of its target genes. In addition, HBV gene expression increased the amount of phosphorylated c-Src kinase.
Treatment with Src kinase inhibitor Dasatinib reduced HBV replication, prevented adherens junction disassembly and reduced β-catenin-signalling, while Sorafenib only did so in cells with mutated β-catenin. Interestingly, none of the HBV induced alterations required HBx. Thus, HBV stimulated β-catenin-signalling and induced disassembly of adherens junctions independently of HBx through Src kinase activation. These pathways may contribute to hepatocellular carcinogenesis and seem to be more efficiently inhibited by Dasatinib than by Sorafenib.