Hepatitis B virus X protein is essential to initiate and maintain virus replication after infection.

Abstract:

The molecular biology of hepatitis B virus (HBV) has been extensively studied but the exact role of the hepatitis B X protein (HBx) in the context of natural HBV infections remains unknown. Primary human hepatocytes and differentiated HepaRG cells allowing conditional trans complementation of HBx were infected with wild type (HBV(wt)) or HBx deficient (HBV(x-)) HBV particles and establishment of HBV replication was followed. We observed that cells inoculated with HBx-deficient HBV particles (HBV(x-)) did not lead to productive HBV infection contrary to cells inoculated with wild type HBV particles (HBV(wt)). Although equal amounts of nuclear covalently closed circular HBV-DNA (cccDNA) demonstrated comparable uptake and nuclear import, active transcription was only observed from HBV(wt) genomes. Trans-complementation of HBx was able to rescue transcription from the HBV(x-) genome and led to antigen and virion secretion, even weeks after infection. Constant expression of HBx was necessary to maintain HBV antigen expression and replication. Finally, we demonstrated that HBx is not packaged into virions during assembly but is expressed after infection within the new host cell to allow epigenetic control of HBV transcription from cccDNA. Our results demonstrate that HBx is required to initiate and maintain HBV replication and highlight HBx as the key regulator during the natural infection process.