Influence of hepatitis B virus genotypes on the intra- and extracellular expression of viral DNA and antigens.

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Abstract

Various genotypes of the hepatitis B virus (HBV) induce liver disease of distinct severity, but the underlying virological differences are not well defined. Huh7 cells were transfected with plasmids carrying 1.24-fold the HBV genome of different genotypes/subgenotypes (2 strains each for Aa/A1, Ae/A2, Ba/B2 and D; 3 each for Bj/B1 and C). HBV DNA levels in cell lysates, determined by Southern hybridization, were the highest for C followed by Bj/Ba and D/Ae ($P < .01$), and the lowest for Aa ($P < .01$), whereas in culture media, they were the highest for Bj, distantly followed by Ba/C/D and further by Ae/Aa ($P < .01$). The intracellular expression of core protein was more than 3-fold lower for Ae/Aa than the others. Hepatitis B e antigen (HBeAg) was excreted in a trend similar to that of HBV DNA with smaller differences. Secretion of hepatitis B surface antigen (HBsAg) was most abundant for Ae followed by Aa, Ba, Bj/C and remotely by D, which was consistent with mRNA levels. Cellular stress determined by the reporter assay for Grp78 promoter was higher for C and Ba than the other genotypes/subgenotypes ($P < .01$). Severe combined immunodeficiency mice transgenic for urokinase-type plasminogen activator (uPA/SCID), with the liver replaced for human hepatocytes, were inoculated with virions passed in mouse and recovered from culture supernatants. HBV DNA levels in their sera were higher for C than Ae by 2 logs during 4-7 weeks after inoculation. In conclusion, virological differences among HBV genotypes were demonstrated both in vitro and in vivo. These differences may influence HBV infections with distinct genotypes in clinical and epidemiological settings.