Hepatitis B virus inhibits the liver regeneration via epigenetic regulation of urokinase-type plasminogen activator

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The liver regeneration after liver damage caused by toxins and pathogens are critical for liver homeostasis. The retardation of liver proliferation was reported in hepatitis B virus (HBV) X protein (HBx)-transgenic mice. However, the underlying mechanism on HBx-mediated disturbance of liver regeneration was not elucidated. Here, we investigated the molecular mechanism on the inhibition of liver regeneration using liver cell lines and mouse model. Liver regeneration after partial hepatectomy (PH) was significantly inhibited in the mice model of hydrodynamic injection of HBx-expressing plasmid. Mice of hydrodynamically injected with HBx or replication-competent wtHBV plasmids showed the prominent reduction in regenerated liver weight than those of the empty vector or HBx-deficient HBV genome. Mechanism studies have revealed that the expression of urokinase-type plasminogen activator (uPA), which regulates the activation of hepatocyte growth factor (HGF), was significantly decreased in liver tissues of HBV or HBx-expressing mice. The down regulation of uPA was further confirmed using liver cell lines transiently or stably transfected with HBx and HBV genome. Furthermore, we demonstrate that HBx represses uPA expression through epigenetic regulation on uPA promoter in mice liver tissues and human liver cell lines. Expression of HBx strongly induced the hypermethylation of uPA promoter through DNMT3A2. Taken together, these data suggest that the infection of HBV can impair the liver regeneration through the epigenetic regulation of liver regeneration signal by HBx.

Keywords: HBV, HBx, liver regeneration, partial hepatectomy, Epigenetic regulation, uPA (형간염바이러스, HBx, 간재생, 후생유전 조절, uPA)