Adriamycin, a Chemotherapeutic drug, Modulates the Expression of HBx Viral Oncoprotein in vitro and in vivo

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**Background** HBx (hepatitis B virus X) viral oncoprotein is a multifunctional transactivator and is thought to play a critical role in the development of liver cancer. However, expression of HBx oncoprotein in HBV-related human liver is actually low and therefore, biological outcomes of HBx in human liver remain obscure. Adriamycin is a commonly used chemotherapeutic drug in transcatheter arterial chemoembolization (TACE) for the patients with unresectable hepatocellular carcinoma. Interestingly, we found that adriamycin significantly enhanced the expression of HBx gene in HBV-related liver cells. In the present study, we elucidated modulation of HBx gene by adriamycin and its biological consequence.

**Methods** HBx-expressing Chang liver cell line (ChangX-34) and HBx-transgenic mice were employed to determine the level of HBx gene after treatment with adriamycin using Western blotting, immunofluorescence staining, Northern blotting and RT-PCR. Changes in the stability of HBx protein upon adriamycin treatment were determined by using pulse-chase labeling method.

**Results** When HBx-expressing ChangX-34 cells were treated with adriamycin, the expression levels of HBx mRNA and protein were dramatically enhanced whereas other chemotherapeutic drugs such as cisplatin and 5-fluorouracil didn’t show any effects. Induction of HBx mRNA was also observed in HBx transgenic mice, which were intraperitoneally administered with adriamycin. Interestingly, increase of HBx mRNA in HBx transgenic mice was accompanied with a significant enhancement of VEGF (vascular endothelial growth factor), implying that angiogenic activity can be also altered in these mice upon adriamycin treatment. In order to understand the mechanism underlying this enhancement of HBx gene expression, changes of the stability of HBx mRNA and protein were determined. We found that degradation of both HBx mRNA and HBx protein was significantly retarded in the presence of adriamycin, resulting in the accumulation of HBx mRNA and protein, respectively.

**Conclusion** Adriamycin enhances the expression of HBx viral oncoprotein in vitro and in vivo by increasing the HBx stability at the levels of both protein and mRNA. Our findings may provide a new insight in developing the rational regimens for TACE.