Expression of HBX, an Oncoprotein of Hepatitis B Virus, Blocks Reoviral Oncolysis of Hepatocellular Carcinoma Cells

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Although reovirus has been used in tests as a potential cancer therapeutic agent against a variety of cancer cells[1], its application to hepatocellular carcinoma cells, in which the hepatitis B virus X (HBX) protein of hepatitis B virus (HBV) plays a primary role[2], has not yet been explored. Here, we describe experiments in which we use reovirus to treat Chang liver carcinoma cells expressing either vector only (Chang-vec) or HBX protein (Chang-HBX). While Chang-vec cells readily support reoviral proliferation and undergo apoptosis, Chang-HBX cells are highly resistant to reoviral infection and virus-induced apoptosis, even though HBX protein induces activation of Ras and inactivation of PKR which normally are thought to enhance reoviral oncolysis. The resistance of Chang-HBX cells to reovirus may instead be explained by HBX-induced down-regulation of Death Receptor 5 and activation of Stat-1. Phosphorylated Stat1 activates ISRE- and GSA-mediated transcription, leading to production of IFN-β, while the reduced expression of Stat1 with its siRNA results in decrease of IFN-β production, by which Chang-HBX cells eventually succumb to reovirus infection. This result further indicates that HBX induces the establishment of an anti-viral state through Stat-1 activation. Thus it appears that active Ras does not override the anti-viral effect mediated by activation of Stat1. Accordingly, we report that HBX, an oncoprotein of HBV, can prevent reoviral oncolysis of hepatocellular carcinoma. This suggests there may be limits to the practical application of reovirus in the treatment of human cancers already expressing other oncoviral proteins.

References

[1] M Kim, YH Chung, and RN Johnston *J. Microbiol*. **45**, 187, 2007

[2] F Azam and A Koulaouzidis *Ann Hepatol.* **7,** 125, 2008