Abstract:

Gene therapy has become an accepted concept for the treatment of a variety of different diseases. In contrast to preclinical models, subjects enrolled in clinical trials, including gene therapy, possess a history of infection with microbes that may influence its safety and efficacy. Especially, viruses that establish chronic infections in the liver, one of the main targets for in vivo gene therapy, raise important concerns. Among them is the hepatitis B virus (HBV), which has chronically infected more than 350 million people worldwide. Here, we investigated the effect of HBV on adeno-associated viral (AAV) vectors, the most frequently applied gene transfer vehicles for in vivo gene therapy. Unexpectedly, we found that HBV greatly improved AAV transduction in cells replicating HBV and identified HBV protein x (HBx) as a key factor. Whereas HBV-positive and -negative cells were indistinguishable with respect to cell-entry efficiency, significantly higher numbers of AAV vector genomes were successfully delivered to the nucleus in the presence of HBV. The HBV-promoting effect was abolished by inhibitors of phosphatidylinositol 3-kinase (PI3K). PI3K was required for efficient trafficking of AAV to the nucleus and
was enhanced in HBV-replicating cells and upon HBx expression. Enhancement of AAV transduction was confirmed in vivo using HBV transgenic mice and could successfully be applied to inhibit HBV progeny release. Conclusion: Our results demonstrate that acute, as well as chronic, infections with unrelated viruses change the intracellular milieu, thereby likely influencing gene therapy outcomes. In the case of HBV, HBx-mediated enhancement of AAV transduction is an advantage that could be exploited for development of novel treatments of HBV infection. (Hepatology 2014; 59:2110-2120).