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A potential approach to treatment of hepatitis B virus infection

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Eukaryotic cells employ multiple strategies of checkpoint signaling and DNA repair mechanisms to monitor and repair damaged DNA. There are two branches in the checkpoint response pathway—ataxia telangiectasia-mutated (ATM) and ATM-Rad3-related (ATR). Many viruses are now known to interact with DNA damage sensing and repair machinery.

These viruses have evolved tactics to eliminate, circumvent, or exploit various aspects of the DNA damage response of the host cell. Strategies include the activation of repair proteins or the targeting of specific cellular factors for degradation or mislocalization. Exploiting the activation of the DNA damage pathway by viral replication for the generation of antiviral drugs needs to be examined.

In the human immunodeficiency virus (HIV), it has been clearly determined that the prevention of viral integration inhibits viral replication and promotes cellular apoptosis. Thus, the ATM-specific inhibitor ku55933 can inhibit HIV replication in primary T cells.

Despite the availability of a safe and efficient vaccine, chronic hepatitis B virus infection remains a major health problem worldwide. Interferon treatment is effective in only approximately one-third of the patients and produces considerable side effects. Long-term treatment with the second-generation nucleoside analogue lamivudine (lam) efficiently inhibits HBV replication with frequent viral polymerase mutations. We found that HBV infection triggered an ATR-dependent DNA damage response,

resulting in increased ATR and Chk1 phosphorylation levels, however, ATR checkpoint signaling was blocked downstream of the p53-dependent pathway to evade apoptosis by p21 degradation. We have designed a strategy to select new drug targets that inhibit a cellular gene required for HBV replication or restore a response stalled by HBV in the ATR DNA damage pathway.

A research article to be published on August 28, 2008 in the *World Journal of Gastroenterology* addresses this question. The research team led by Professor, Zhong from Beijing Institute of Biotechnology used report that HBV infection activates and exploits the DNA damage response to replication stress. They investigated whether the inhibition of DNA damage response by CF, TP and UCN01 or the restoration of p21 expression by p21 transfection or proteasome inhibition would lead to suppressed HBV replication.

They set up a chronic HBV infection model by culturing hepatocyte HL7702 cells with HBV-positive serum without washing off input virus as conventional. HBV DNA titers inside the infected cells represent the final viral amount including the infected DNA without being degraded and the newly synthesized HBV DNA. In this way, studying the efficacy of DNA damage response inhibitors on HBV infection and replication was available. In addition, since DNA damage response is an acute response that happens quickly after virus infection, they assume that early intervention of DNA damage pathway will function more efficiently, thus can be used clinically as HBV infection therapy during its early infectious stage or fulminant HBV infection.

Source: World Journal of Gastroenterology