Novel therapeutic approaches to cure chronic HBV infection

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Exciting new data presented today at the International Liver Congress 2013 include results from early in vitro and in vivo studies targeting covalently closed circular DNA (cccDNA), which may form the basis of a cure for chronic hepatitis B virus (HBV) infection.

HBV cccDNA is organized into mini-chromosomes within the nucleus of infected cells by histone and non-histone proteins. Despite the availability of efficient therapies against HBV, long-term persistence of cccDNA necessitates life-long treatments to suppress the virus. The following three experimental studies demonstrate effective HBV-cccDNA targeting/depletion using novel therapeutic approaches which offer the potential of a cure.

Liver regeneration induces strong reduction of viral replication and cccDNA levels, but not complete cccDNA eradication; without antiviral treatment, de novo HBV infection can be re-established.

Key findings of research in HBV-infected human hepatocytes using the uPA/SCID chimeric mouse system show that liver regeneration induces strong reduction of viral replication and cccDNA levels, with rapid formation of cccDNA-free hepatocytes. However, because complete cccDNA eradication is not achieved, in the absence of antiviral treatment, de novo HBV infection could be re-established in quiescent (non-dividing) human hepatocytes. This suggests that induction of hepatocyte turn-over together with antiviral drugs inducing viral suppression, such as nucleoside analogues and IFN, or blocking cell entry, may accelerate the clearance of the viral minichromosome.

Targeting epigenetic control of nuclear cccDNA minichromosome to suppress HBV transcription and replication may form basis for other therapeutic approaches to curing chronic HBV infection.

In the infected liver cell the rate of replication of HBV is regulated by the acetylation or methylation of histone proteins which surround the cccDNA minichromosome – so called epigenetic regulation. In a separate innovative study, the suppression of HBV transcription and replication by small molecules that target the epigenetic control of nuclear cccDNA minichromosome was investigated. The different classes of small molecules studied included: Class I, II and III histone deacetylase inhibitors (HDACi); p300 and PCAF histone acetyltransferases (HAT) inhibitors; hSirt1 activators; JMJD3 histone demethylase inhibitors.

The combined inhibition of p300 and PCAF HATs resulted in an evident reduction of HBV replication which mirrored the decrease of pgRNA transcription. The hSirt1/2 activator MC2791 and the JMJD3 inhibitor MC3119, albeit with different efficiency, inhibited both HBV replication and cccDNA transcription. Results represent a proof of concept that activation of hSirt1 and Ezh2 (through the inhibition of its functional antagonist JMJD3) by small molecules can induce an active epigenetic suppression of HBV cccDNA minichromosome similar to that observed with IFN?, and lead to persistent cccDNA silencing.

Lymphtoxin beta receptor (LTbR) agonisation represents basis for novel alternative therapeutic approach to curing chronic HBV infection.

The final study demonstrated that stimulating the lymphtoxin beta receptor (LTbR) provides an effective, long lasting and non-cytopathic mechanism for achieving effective HBV-cccDNA depletion in infected hepatocytes. Cell culture models including HBV-infected HepaRG cells and primary human hepatocytes were used to test the effect of antibodies stimulating human LTbR (BS1 or CBE11). Results show that a strong and dose-dependent anti-HBV effect was achieved by activation of the LTbR. All HBV replication markers

were decreased with this treatment, including cccDNA in cells where HBV infection was already established.

Hepatitis B is the most prevalent cause of chronic viral hepatitis and a major global health problem. Prof. Fabien Zoulim, EASL Educational Councillor commented on the exciting new data: "In chronic hepatitis B infection, the viral genome forms a stable minichromosome - the covalently closed circular DNA (cccDNA) - which can persist throughout the lifespan of the hepatocyte."

"Current treatments focus on suppression of HBV and discovery of compounds directly targeting cccDNA has been one of the major challenges to curing HBV infection; but these preliminary data show novel therapeutic approaches can be applied to successfully target cccDNA with the long-term aspiration of finding a cure" added Prof. Fabien Zoulim.

More information: References:

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3 MOLECULES THAT TARGET THE EPIGENETIC CONTROL OF NUCLEAR CCCDNA MINICHROMOSOME. Presented at the International Liver Congress 2013 4 Lucifora J et al, LYMPHOTOXIN BETA RECEPTOR ACTIVATION LEADS TO DEGRADATION OF HBV CCCDNA FROM INFECTED HEPATOCYTES. Presented at the International Liver Congress 2013

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