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Abstract

Identification of Aquarius and Senataxin as Restriction Host Factors for Hepatitis B Virus Infection †

Christina Whitten-Bauer [1], Andoni Gómez-Moreno [2] and Urtzi Garaigorta [1,2,*]

[1] The Scripps Research Institute (TSRI), La Jolla, CA 92037, USA; whittencr@gmail.com
[2] Centro Nacional de Biotecnología-Consejo Superior de Investigaciones Científicas (CNB-CSIC), 28049 Madrid, Spain; agomez@cnb.csic.es
* Correspondence: ugaraigorta@cnb.csic.es
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Abstract: Hepatitis B virus (HBV) represents an important human pathogen causing acute and chronic hepatitis. Over 240 million people are chronically infected, many of whom will die due to complications such as liver cirrhosis and hepatocellular carcinoma. Currently approved therapies are very effective in suppressing virus replication and viremia, but they are not curative, because they do not completely eliminate the nuclear episomal DNA form of HBV (cccDNA) that re-establishes infection upon interruption of therapy. Despite our understanding of many aspects of the HBV lifecycle, details of the HBV cccDNA biology remain poorly understood. Our group is pursuing a loss-of-function genetic screening approach, to identify cellular factors regulating HBV infection. A lentivirus-delivered short hairpin RNA (shRNA) library, composed of 384 shRNAs, was used to interrogate the function of 80 DNA damage repair pathway proteins in the establishment of HBV infection. The primary screening identified 10 cellular factors that regulate the HBV infection both positively or negatively. Two of those proteins, aquarius (AQR) and senataxin (SETX), were subsequently validated as factors restricting the HBV infection in independent experiments. Silencing of AQR and SETX led to an increased infection efficiency that was characterized by higher intracellular levels of HBV cccDNA, HBV mRNA, and core protein, and increased HBV e antigen (HBeAg) accumulation in the supernatants of infected cells. The expression level, glycosylation pattern, and localization of the HBV receptor, sodium taurocholate cotransporting polypeptide (NTCP), in AQR- and SETX-downregulated cells was equivalent to that of the control cells. Collectively, our results are compatible with AQR and SETX restricting early steps in the HBV lifecycle and downstream HBV entry, that affect the establishment of the HBV cccDNA pool. Experiments to unravel the function of these proteins in the context of HBV infection are currently underway.

Keywords: hepatitis B virus; restriction factors; aquarius; senataxin

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