cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Reverse Cholesterol Transport of Macrophages Repurposed for Hepatitis B Virus Entry

Whereas hepatitis B virus (HBV) is known to infect hepatocytes in vivo with exceptionally high efficiency,[1] it remains to be understood why HBV infection of cultured hepatocytes expressing its cellular receptor taurocholate cotransporting polypeptide (NTCP) is much less efficient and takes a longer time.[2] It is thought that the histologic structure and the other types of cells in the hepatic microenvironment may also facilitate HBV entry into hepatocytes. Indeed, NTCP is a protein in the sinusoidal-basolateral membrane of hepatocytes. After reaching hepatic sinusoidal capillary, HBV needs to cross a protective barrier formed by liver sinusoidal endothelial cells (LSECs) to enter the space of Disse, where HBV accesses the sinusoidal–basolateral membrane of the hepatocytes to infect them through NTCP.[3] In another perspective, LSECs are liver-resident antigen-presenting cells that can uptake HBV and then release it to infect adjacent hepatocytes as proposed in the model of duck HBV.[4]

Lipoproteins are protein-lipid complexes transporting insoluble lipids around the body. Based on size and composition, lipoproteins can be classified into 6 classes: chylomicrons (CMs), CM remnants, very-low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs; also known as VLDL remnants), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs). The removal of triglycerides from CMs and VLDLs by lipoprotein lipase results in the formation of CM remnants and VLDL remnants, respectively. The further removal of triglycerides from VLDL remnants results in the formation of LDLs.[5] The liver is the most crucial organ for lipoprotein clearance. The liver clears CM remnants, VLDL remnants, and most LDLs (approximately 70%) through receptor-mediated endocytosis. For HDL catabolism, the liver not only receives almost all HDL-carried cholesterols, which are reversely transported from peripheral tissues, but also degrades a part of HDL particles.[6] Fat-laden macrophages, such as hepatic Kupffer cells, also efflux cholesterol to hepatocytes through reverse lipid transport. Apolipoprotein E (Apo-E) is a key apolipoprotein present in CM remnants, VLDL remnants, and a subgroup of HDLs. Apo-E mediates hepatic uptake of these lipoproteins by binding to LDL receptor and related receptors on hepatocytes.[7]

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Esser et al[8] developed an ex vivo liver perfusion and infection model. Using this model, they characterized early steps of HBV uptake into the liver under physiological conditions. HBV appeared in liver macrophages at 1 hour postinfection but was detected in hepatocytes only at 16 hours postinfection. HBV bound to Apo-E-rich lipoproteins in human serum and entered liver macrophages through receptor-mediated lipoprotein endocytic pathway. Within liver macrophages, HBV was found to move to recycling endosomes by hijacking the recycling transport of cholesterol or lipoproteins, and to accumulate there. Sorting to recycling endosomes avoided HBV trafficking to lysosomes for degradation. HBV usurped the reverse cholesterol transport pathway to return to the cell surface of macrophages, where its transmission to hepatocytes occurred through intracellular membrane bridges.[8]

An interesting framework for how HBV establishes early infection in the liver has been put forward in this study. First, hepatocytes are transinfected by HBV via liver macrophages. This route might be important and could at least partially explain the efficiency difference between in vivo and in vitro infection. Transcytosis of liver macrophages could help HBV to bypass the LSEC barrier to infect hepatocytes.[1,8] Second, the study also unveils the role of reverse cholesterol transport pathway of hepatic macrophages in HBV infection. Usurpation of a liver-specific mechanism for lipoprotein clearance could be another reason for HBV hepatotropism besides NTCP. Third, the report reveals a new facet of the interplay among HBV, lipids, and lipoproteins in the context of viral entry. Lipids including cholesterol are important to viral life cycle. Viruses are known to target lipid signaling, transport, and metabolism to favor their own replication.[9] It will be of interest to see whether other hepatotropic viruses, such as hepatitis C virus, might also repurpose macrophage reverse cholesterol transport for viral entry. Finally, an ex vivo HBV infection model has been established. The direct use of human tissues in this model ensures the investigation of HBV infection under physiologically relevant condition.[8] This is a valuable addition to the tool box for analysis of HBV infection.[10]

Going forward, 4 additional areas of research are worthy of further exploration. First, it is still not clear how HBV associates with the Apo-E-rich lipoprotein. Is HBV physically interacting with Apo-E? If not, which HBV components and lipoprotein components mediate such association? Second, hepatocytes are the major cells clearing lipoproteins. It is interesting to explore whether HBV can infect hepatocytes through the lipoprotein endocytic pathway directly without the help of NTCP. Third, HBV seems to use multiple lipid transport pathways to transcytose across macrophages, including receptor-mediated lipoprotein endocytosis, selective sorting into recycling endosomes, and cholesterol efflux. The mechanism by which HBV hijacks these pathways should be further explored. Finally, important questions concerning the interplay between HBV and LSECs should be addressed. Can LSECs also uptake HBV and pass on to hepatocytes as in the duck model?[4] If yes, can it also be

mediated through reverse cholesterol transport? If no, to what extent can transcytosis of HBV from liver macrophages help to bypass the LSEC barrier? Addressing these questions might lead to another breakthrough in the field.

YUN CHENG
TAO CHENG
DONG-YAN JIN
School of Biomedical Sciences
Li Ka Shing Faculty of Medicine
The University of Hong Kong
Pokfulam, Hong Kong

References

1. Asabe S, Wieland SF, Chattopadhyay PK, et al. The size of the viral inoculum contributes to the outcome of hepatitis B virus infection. J Virol 2009;83:9652–9562.
2. Yan H, Zhong G, Xu G, et al. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. Elife 2012;1:e00049.
3. Tian J, Li C, Li W. Entry of hepatitis B virus: going beyond NTCP to the nucleus. Curr Opin Virol 2021;50:97–102.
4. Breiner KM, Schaller H, Knolle PA. Endothelial cell-mediated uptake of a hepatitis B virus: a new concept of liver targeting of hepatotropic microorganisms. Hepatology 2001;34:803–808.
5. Feingold KR. Lipid and lipoprotein metabolism. Endocrinol Metab Clin North Am 2022;51:437–458.
6. Zanoni P, Velagapudi S, Yalcinkaya M, et al. Endocytosis of lipoproteins. Atherosclerosis 2018;275:273–295.
7. Ouimet M, Barrett TJ, Fisher EA. HDL and reverse cholesterol transport. Circ Res 2019;124:1505–1518.
8. Esser K, Cheng X, Wettengel JM, et al. Hepatitis B virus targets lipid transport pathways to infect hepatocytes. Cell Mol Gastroenterol Hepatol 2023;16:201–221.
9. Heaton NS, Randall G. Multifaceted roles for lipids in viral infection. Trends Microbiol 2011;19:368–375.
10. Li F, Wang Z, Hu F, et al. Cell culture models and animal models for HBV study. Adv Exp Med Biol 2020;1179:109–135.

Correspondence
Address correspondence to: Dong-Yan Jin, PhD, School of Biomedical Sciences, LKS Faculty of Medicine, The University of Hong Kong, 3/F Laboratory Block, 21 Sassoon Road, Pokfulam, Hong Kong. e-mail: dyjin@hku.hk.

Conflicts of interest
The authors disclose no conflicts.


Most current article

2352-345X
https://doi.org/10.1016/j.jcmgh.2023.05.004