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EDITORIAL

Back to the Roots: Noncanonical Retrograde Trafficking of the HBV Nucleocapsids

The biology of hepatitis B virus (HBV) has been studied extensively, however, there are still a variety of open questions with respect to its life cycle. Even steps that seemed to be clear turn out to be more complex than initially assumed. A good example of this is the release of viral and subviral particles from HBV-infected cells. HBV is a small DNA virus that infects with a very high tissue- and species-specificity human hepatocytes. The HBV nucleocapsid harbors a partially double-stranded circular DNA genome. During the infection process, the genome is delivered into the nucleus and converted to a covalently closed circular molecule (cccDNA), a very stable and long-lived minichromosomeKlicken oder tippen Sie hier, um Text einzugeben.[1] The high stability and persistence of cccDNA represents a major obstacle for the cure of a chronic HBV infection.[2] It is well established that HBV is internalized by receptor-mediated endocytosis and either after a fusogenic process triggered by the membrane proteins of HBV, or by a membrane-permeable peptide motif within the HBV surface proteins, the nucleocapsid is released into the cytoplasm. Based on in vitro studies and microinjection of purified HBV capsids into *Xenopus* oocytes, dynein light chain LL1 was found to interact with the nucleocapsid and to mediate the directed transport by microtubules to the nuclear pore complex.[3] However, this pathway bears certain risks regarding inefficient escape from the late endosome/endolysosome, leading to lysosomal degradation of the nucleocapsid. Moreover, the transfer through the cytoplasm increased the accessibility to innate immune mechanisms.

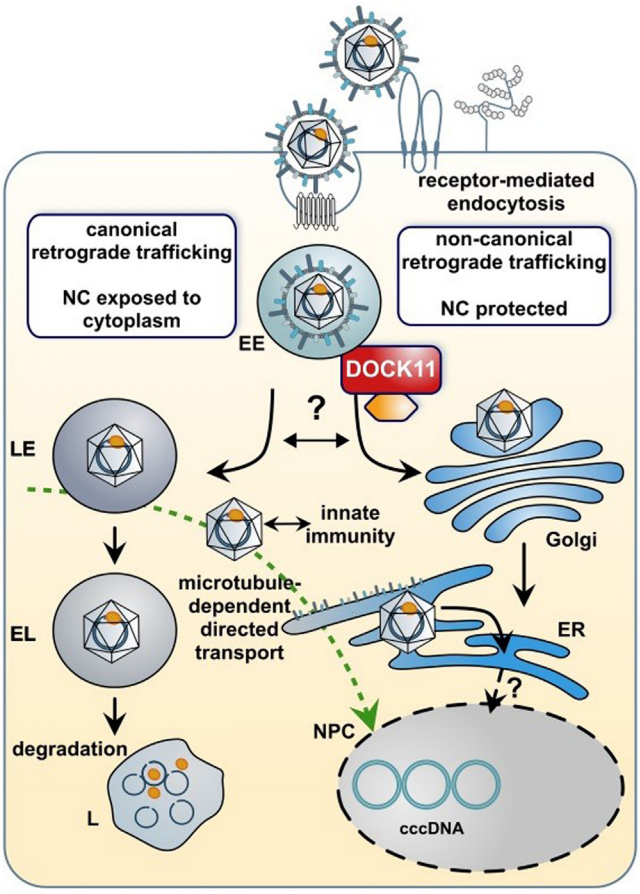

Figure 1. Retrograde trafficking of HBV nucleocapsid is facilitated by DOCK11. EE, early endosome; EL, endolysosome; ER, endoplasmic reticulum; L, lysosome; LE, late endosome; NC, nucleocapsid; NPC, nuclear pore complex.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Li et al[4] describe a mechanism of noncanonical retrograde trafficking of the HBV capsid. They identify dedicator of cytokinesis 11 (DOCK11) in complex with ankyrin repeat and PH domain-containing protein 2 (AGAP2) and adenosine diphosphate-ribosylation factor 1 (ARF1) as a central factor for the retrograde trafficking via the early endosome trans-Golgi network endoplasmic reticulum for intracellular transport of HBV nucleocapsids toward the nuclear pore complex. In the complex, DOCK11 shows guanine nucleotide exchange factor activity and AGAP2 shows guanosine triphosphatase-activating protein activity toward ARF1 (Figure 1). The continuous activation of ARF1 by DOCK11 and the deactivation by AGAP2 could facilitate recycling of vesicles. Moreover, DOCK11 can bind to capsids and thereby recruit the capsids for retrograde trafficking. There is a clear correlation between the amount of DOCK11 and the level of cccDNA. This extends previous reports describing the relevance of DOCK11 for cccDNA formation[5,6] and raises the question of whether DOCK11 could be a target for novel strategies to cure chronic HBV infection by elimination of cccDNA.

Considering the very small number of HBV particles that are internalized in the infection process, the use of a protected environment for the intracellular trafficking of the nucleocapsid toward the nucleus also could facilitate the establishment of an infection. In light of this, it is interesting that Li et al[4] observed that Ras-related protein Rab-7a (RAB7A) is not necessary for HBV infection. In contrast, RAB7A knockout cells were found to be more susceptible for HBV infection, arguing for a pathway independent from late endosomes and endolysosomes.

The transport of de novo synthesized nucleocapsids back to the nucleus increases levels of intranuclear cccDNA. In light of the longevity of cccDNA, an overflow has to be avoided. This could be fulfilled by preferential use of the RAB7A-dependent lysosomal pathway. Thus, an interesting

question is about the mechanisms in a later period of infection regulating the equilibrium between the canonical and the noncanonical retrograde trafficking of nucleocapsid transport to the nucleus.

A second interesting question is the mechanism of HBV-dependent up-regulation of DOCK11 expression. Which signaling cascades are involved in this process? What is the impact of HBx and the PreS2 activator large hepatitis B virus surface protein on the expression of DOCK11? Apart from the amount of DOCK11, a further target for regulation of this process could be the stability of the DOCK11 ARF1 and AGAP2 interaction. Moreover, it will be interesting to study the impact of nucleocapsid modifications on the interaction with DOCK11—this could be a mechanism conferring selectivity in this process. Last but not least, there is the question about the final escape of the nucleocapsid from the endoplasmic reticulum and its import. In conclusion, this very interesting report shows us again that answering one question about HBV life cycle raises several novel questions that can be addressed in future studies.

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Conflicts of interest
The authors disclose no conflicts.


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