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Hot Topic Commentary

SCARF2 Mediates Intracellular Trafficking and Nucleocapsid Release of Hepatitis B Virus Within Hepatocytes

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Knowledge Gaps in the hepatitis B virus (HBV) Life Cycle: Barriers to Functional Cure

In the early 1960s, the discovery of hepatitis B surface antigen (HBsAg), initially termed the Australia antigen, by Baruch S. Blumberg marked a milestone that enabled the diagnosis of acute and chronic hepatitis B (CHB) and the development of vaccines against HBV infection. Due to his great contribution, he received the Nobel Prize in Physiology or Medicine in 1976.[1] To date, HBV infection remains a major global public health challenge, affecting approximately 257.5 million people worldwide[2] and leading to chronic liver diseases such as cirrhosis and hepatocellular carcinoma. The HBV genome encodes three structurally related envelope proteins—the large, middle, and small surface proteins—through the preS1, preS2, and S regions. Clinically, functional cure of CHB is generally defined by sustained loss of serum HBsAg, with or without the development of antibodies to HBsAg, following antiviral treatment. Chronic hepatitis C virus infection can now be cured with direct-acting antiviral agents.[3] However, achieving a functional cure remains difficult for patients with CHB. Currently available antiviral agents and immunomodulatory drugs can suppress viral replication but rarely induce HBsAg clearance,[4] with only a minority of patients achieving functional cure. During HBV infection, following viral attachment and internalization into hepatocytes, HBV delivers its relaxed circular DNA (rcDNA) into the nucleus, where it is converted into covalently closed circular DNA (cccDNA). As the transcriptional template for viral replication and antigen synthesis, cccDNA and integrated HBV DNA represent major obstacles to achieving a functional cure of CHB.[4,5] Despite extensive investigation over the past several decades, many critical steps of the HBV life cycle remain incompletely understood, particularly the molecular mechanisms regulating viral entry into hepatocytes and the subsequent intracellular events that support productive infection and viral persistence.

The identification of sodium taurocholate cotransporting polypeptide (NTCP) as a functional receptor for HBV entry in 2012 represented a major breakthrough in HBV research,[6] greatly advancing understanding of HBV entry into hepatocytes. HBV entry is a highly coordinated multistep process involving viral attachment, internalization and intracellular trafficking, and nuclear delivery. Initially, HBV virions bind to host heparan sulfate proteoglycans (HSPGs) on the hepatocyte surface through the S domain in a low-affinity, nonspecific manner.[7] Subsequently, the preS1 domain of the large HBV surface protein specifically binds NTCP, triggering viral internalization into hepatocytes.[6,8,9] Notably, naturally occurring genetic variants of NTCP may alter its interaction with the preS1 domain and consequently influence host susceptibility to HBV infection. After binding to NTCP, HBV is internalized through endocytosis, a process reported to depend on NTCP ubiquitination,[10] and to be triggered by epidermal growth factor receptor (EGFR) signaling.[11] The internalized virions are subsequently transported toward the nuclear envelope and ultimately delivered to the nucleus. However, the molecular mechanisms governing post-entry events, including intracellular trafficking, nucleocapsid uncoating, and nuclear import, remain incompletely understood.[12]

Identification of Scavenger receptor class F member 2 (SCARF2) Expands Understanding of the HBV Life Cycle

SCARF2 is a member of the scavenger receptor family. Homozygous mutations in SCARF2 were previously found to be responsible for Van den Ende–Gupta syndrome.[13,14] Li *et al.* recently identified SCARF2 as an intracellular receptor that facilitates the transport of HBV-containing endosomes to nuclear pore complexes (NPCs) and promotes HBV nucleocapsid release from endosomes (Fig. 1).[15] These findings provide important mechanistic insights into the poorly understood post-entry stages of the HBV life cycle. Using a targeted functional screen of membrane proteins specifically expressed in hepatocytes, the investigators demonstrated that SCARF2 is required for efficient post-entry trafficking following NTCP-mediated internalization. Depletion of SCARF2 markedly reduced HBV infection in HepG2-NTCP and HepaRG cells, whereas overexpression of SCARF2 increased susceptibility to HBV infection. Notably, SCARF2 appeared to function specifically during the early stages of

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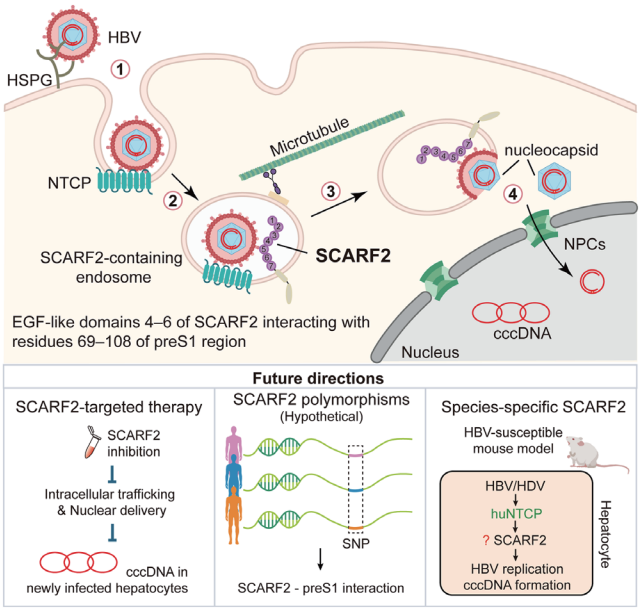

Fig. 1. Proposed roles of SCARF2 in HBV infection and therapeutic implications. Top: HBV enters hepatocytes through a highly coordinated multistep process. Step 1: HBV binds to cellular HSPGs on hepatocytes, followed by specific binding to NTCP, thereby mediating HBV attachment to hepatocytes. Step 2: HBV virions are internalized through endocytosis. Step 3: SCARF2-containing endosomes transport internalized HBV along microtubules to the cytoplasmic side of NPCs through interactions between EGF-like domains 4–6 of SCARF2 and residues 69–108 of the HBV preS1 region. Step 4: SCARF2 facilitates the endosomal release of HBV nucleocapsids. Bottom: Therapeutic implications and future perspectives of SCARF2 in HBV infection. SCARF2 inhibitors could be explored as a strategy to prevent *de novo* HBV infection (left). Hypothetical genetic alterations in SCARF2 may potentially alter the interaction between SCARF2 and preS1 (middle). Species-specific differences in SCARF2 may inform the development of HBV-susceptible mouse models (right). cccDNA, covalently closed circular DNA; EGF, epidermal growth factor; HBV, hepatitis B virus; HSPGs, heparan sulfate proteoglycans; NPCs, nuclear pore complexes; NTCP, sodium taurocholate cotransporting polypeptide; SCARF2, scavenger receptor class F member 2.

infection, as modulation of SCARF2 expression had minimal impact once infection was established. Mechanistically, SCARF2 directly interacts with HBV particles during intracellular trafficking. Biochemical and mutagenesis analyses revealed that the extracellular epidermal growth factor-like domains 4–6 of SCARF2 bind the preS1 region of the HBV large envelope protein, with amino acids 69–108 constituting the major binding region. Residue 90 was particularly important for SCARF2 recognition, as its mutation substantially impaired SCARF2 binding and reduced viral infectivity, indicating that the SCARF2–preS1 interaction is important for productive HBV infection. Advanced imaging and trafficking analyses revealed that internalized HBV particles are incorporated into SCARF2-containing endosomal vesicles shortly after entry. These SCARF2-positive vesicles subsequently move toward the perinuclear region and accumulate near NPCs. Electron microscopy and colocalization analyses demonstrated that viral particles are enriched on the cytoplasmic side of NPCs, suggesting that SCARF2-containing endosomes may function as specialized carriers that transport internalized HBV to NPCs. Loss of SCARF2 significantly impaired the accumulation of viral particles near NPCs, indicating that SCARF2 is required for efficient intracellular targeting of incoming virions. Importantly, SCARF2 promotes the release of HBV nucleocapsids from endosomal compartments. Knockdown of SCARF2 resulted in a marked reduction in HBV nucleocapsid release efficiency, thereby limiting the delivery of rcDNA to the nucleus and subsequent formation of cccDNA. Collectively, these findings support a model in which SCARF2 acts as an intracellular receptor downstream of NTCP, coupling endosomal trafficking with nucleocapsid release and thereby facilitating productive infection.

These findings provide important insights into how HBV particles are transported to NPCs and how HBV nucleocapsids escape from endosomal compartments after entry into hepatocytes. Together with previous findings identifying NTCP as a key mediator of viral attachment and internalization, the discovery of SCARF2 supports a sequential model of HBV entry: HBV initially attaches to HSPGs, followed by high-affinity engagement of NTCP through the viral preS1 domain; activation of EGFR-dependent endocytosis facilitates viral internalization; and SCARF2 functions downstream of NTCP to direct intracellular trafficking and facilitate nucleocapsid release from endosomal compartments. This stepwise mechanism further refines the current framework of HBV entry biology.

SCARF2 as a Potential Therapeutic Target for HBV Infection

SCARF2 may therefore represent a potential host target for preventing *de novo* HBV infection. First, the identification of SCARF2 as an intracellular receptor for HBV has important implications for antiviral drug development. Current therapeutic strategies for CHB remain unable to efficiently eliminate cccDNA. The study demonstrated that SCARF2 contributes indirectly to cccDNA formation in newly infected hepatocytes by promoting viral trafficking and nucleocapsid release, suggesting that targeting SCARF2 might inhibit HBV infection at a stage downstream of NTCP-mediated internalization and thereby limit the establishment of persistent infection. Notably, the therapeutic benefit of SCARF2-targeted interventions may be greatest for preventing *de novo* infection, limiting viral spread to uninfected hepatocytes, and reducing reinfection after cccDNA clearance.

Second, genetic variation in SCARF2 may influence HBV infection. A well-characterized single-nucleotide polymorphism in the NTCP gene (*SLC10A1*), resulting in the S267F substitution, has been associated with resistance to HBV infection in a large Han Chinese cohort. Mechanistically, this protective effect may result from impaired ligand binding to NTCP, reducing its function as a receptor for HBV entry into hepatocytes.[16] Accordingly, because SCARF2 directly interacts with the preS1 region of the HBV large surface protein and plays an important role in cccDNA establishment, naturally occurring genetic variants within the SCARF2 locus may theoretically influence individual susceptibility to HBV infection, viral persistence, and treatment outcomes. Systematic genetic and epidemiological studies will therefore be important for defining the clinical significance of SCARF2 polymorphisms in diverse populations.

Finally, the clinical development of the NTCP-targeting entry inhibitor bulevirtide provides proof of concept for host-targeted antiviral strategies.[17] The study demonstrated that disruption of SCARF2 function markedly impairs HBV trafficking to NPCs, nucleocapsid release, and cccDNA formation, highlighting multiple potentially vulnerable steps in the viral life cycle. Analogous to NTCP inhibition, therapeutic approaches targeting SCARF2—such as small-molecule inhibitors or agents that disrupt the SCARF2–preS1 interaction—may offer a novel strategy to prevent *de novo* HBV infection, block cccDNA establish-

ment, and support prophylactic or early-intervention strategies against HBV infection.

Despite its therapeutic potential, the physiological functions of SCARF2 should be carefully considered during drug development. Given the essential role of SCARF2 in normal human development and the fact that homozygous mutations cause Van den Ende–Gupta syndrome, future therapeutic strategies may raise safety concerns and should preferentially focus on liver-targeted delivery, transient inhibition during the early stages of HBV infection, or selective disruption of the SCARF2–HBV interaction. Systematic assessment of safety and therapeutic feasibility will be needed to minimize interference with the physiological functions of SCARF2 while maintaining antiviral efficacy.

Beyond its therapeutic implications, SCARF2 may also be relevant to the development of HBV animal models. A recent study showed that the dominant restriction to HBV infection in murine hepatocytes expressing human NTCP occurs at a late entry step preceding nucleocapsid uncoating.[18] Because SCARF2 mediates intracellular trafficking and nucleocapsid release, species-specific differences in SCARF2 expression or function may contribute to this restriction. Comparative studies of human and murine SCARF2 may therefore provide insights to facilitate the development of HBV-susceptible mouse models.

Conclusions

In conclusion, the study by Li *et al.* identifies SCARF2 as an important host factor involved in HBV intracellular trafficking and nucleocapsid release in hepatocytes. By revealing a molecular mechanism through which SCARF2 mediates transport of HBV-containing endosomes to NPCs, the study advances understanding of post-entry events in the HBV life cycle and refines existing models of viral infection. The SCARF2–HBV interaction may represent a potential target for future therapeutic development against HBV infection.

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Conflict of interest

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Author contributions

Drafting the manuscript (SYC); critical revision of the manuscript, intellectual input, and supervision (FSW). Both authors read and approved the final manuscript.

References

[1] Marsh RF. The 1976 nobel prize for physiology or medicine. Science 1976;194(4268):927–929. doi:10.1126/science.194.4268.927, PMID:17748546.
[2] Polaris Observatory Collaborators. Global prevalence, cascade of care, and prophylaxis coverage of hepatitis B in 2022: a modelling study. Lancet Gastroenterol Hepatol 2023;8(10):879–907. doi:10.1016/S2468-1253(23)00197-8, PMID:37517414.
[3] Manns MP, Maasoumy B. Breakthroughs in hepatitis C research: from discovery to cure. Nat Rev Gastroenterol Hepatol 2022;19(8):533–550. doi:10.1038/s41575-022-00608-8, PMID:35595834.
[4] Yuen MF, Chen DS, Dusheiko GM, Janssen HLA, Lau DTY, Locarnini SA, *et al*. Hepatitis B virus infection. Nat Rev Dis Primers 2018;4:18035. doi:10.1038/nrdp.2018.35, PMID:29877316.
[5] Feld JJ, Gehring AJ, Zoulim F. Getting to HBV cure-Will new biomarkers help? Hepatology 2026;84(2):582–600. doi:10.1097/HEP.0000000000001334, PMID:40168396.
[6] Yan H, Zhong G, Xu G, He W, Jing Z, Gao Z, *et al*. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. Elife 2012;1:e00049. doi:10.7554/eLife.00049, PMID:23150796.
[7] Schulze A, Gripon P, Urban S. Hepatitis B virus infection initiates with a large surface protein-dependent binding to heparan sulfate proteoglycans. Hepatology 2007;46(6):1759–1768. doi:10.1002/hep.21896, PMID:18046710.
[8] Asami J, Kimura KT, Fujita-Fujiharu Y, Ishida H, Zhang Z, Nomura Y, *et al*. Structure of the bile acid transporter and HBV receptor NTCP. Nature 2022;606(7916):1021–1026. doi:10.1038/s41586-022-04845-4, PMID:35580629.
[9] Kobayashi C, Ekimoto T, Ooka K, Mifune J, Matsuzawa K, Que L, *et al*. Multistep receptor binding of the hepatitis B virus preS1 domain. Nat Commun 2026;17(1):102. doi:10.1038/s41467-025-68062-z, PMID:41617687.
[10] Appelman MD, Nguyen TA, Oswald A, Lucko A, Paulusma CC, Protzer U, *et al*. NTCP ubiquitination enables HBV infection. JHEP Rep 2025;7(11):101534. doi:10.1016/j.jhepr.2025.101534, PMID:41127880.
[11] Iwamoto M, Saso W, Sugiyama R, Ishii K, Ohki M, Nagamori S, *et al*. Epidermal growth factor receptor is a host-entry cofactor triggering hepatitis B virus internalization. Proc Natl Acad Sci U S A 2019;116(17):8487–8492. doi:10.1073/pnas.1811064116, PMID:30952782.
[12] Watashi K, Shionoya K, Kobayashi C, Morita T. Hepatitis B and D virus entry. Nat Rev Microbiol 2025;23(5):318–331. doi:10.1038/s41579-024-01121-2, PMID:39572840.
[13] Ishii J, Adachi H, Aoki J, Koizumi H, Tomita S, Suzuki T, *et al*. SREC-II, a new member of the scavenger receptor type F family, trans-interacts with SREC-I through its extracellular domain. J Biol Chem 2002;277(42):39696–39702. doi:10.1074/jbc.M206140200, PMID:12154095.
[14] Anastasio N, Ben-Omran T, Teebi A, Ha KC, Lalonde E, Ali R, *et al*. Mutations in SCARF2 are responsible for Van Den Ende-Gupta syndrome. Am J Hum Genet 2010;87(4):553–559. doi:10.1016/j.ajhg.2010.09.005, PMID:20887961.
[15] Li C, Wang Y, Xiong R, Li Q, Zhou Z, Liu Q, *et al*. Scavenger receptor class F member 2 is an intracellular receptor for hepatitis B virus. Cell 2026;189(14):4454–4470.e9. doi:10.1016/j.cell.2026.04.045, PMID:42167249.
[16] Peng L, Zhao Q, Li Q, Li M, Li C, Xu T, *et al*. The p.Ser267Phe variant in SLC10A1 is associated with resistance to chronic hepatitis B. Hepatology 2015;61(4):1251–1260. doi:10.1002/hep.27608, PMID:25418280.
[17] Liu H, Zakrzewicz D, Nosol K, Irobalieva RN, Mukherjee S, Bang-Sørensen R, *et al*. Structure of antiviral drug bulevirtide bound to hepatitis B and D virus receptor protein NTCP. Nat Commun 2024;15(1):2476. doi:10.1038/s41467-024-46706-w, PMID:38509088.
[18] Hong X, Brousseau G, Chen HA, Freije CA, Seifert LL, Zhang M, *et al*. Hepatitis B virus covalently closed circular DNA formation in murine hepatic cells uncovers a late entry block. Proc Natl Acad Sci U S A 2026;123(17):e2603476123. doi:10.1073/pnas.2603476123, PMID:42012961.