Johannes Roksund Hov

Norwegian PSC Research Center and Research Institute of Internal Medicine and Section of Gastroenterology, Division of Surgery, Inflammatory Diseases and Transplantation, Oslo University Hospital and University of Oslo, Oslo, Norway
Email: j.e.r.hov@medisin.uio.no

ORCID

Johannes Roksund Hov https://orcid.org/0000-0002-5900-8096

REFERENCES

1. Kinoshita Y, Ishimura N, Ishihara S. Advantages and disadvantages of long-term proton pump inhibitor use. *J Neurogastroenterol Motil*. 2018;24:182-196.
2. Min YW, Kang D, Shin J-Y, et al. Use of proton pump inhibitors and risk of cholangitis: a nationwide cohort study. *Aliment Pharmacol Ther*. 2019;50:760-768.
3. Lo WK, Chan WW. Proton pump inhibitor use and the risk of small intestinal bacterial overgrowth: a meta-analysis. *Clin Gastroenterol Hepatol*. 2013;11:483-490.
4. Zhernakova A, Kurilshikov A, Bonder MJ, et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. *Science*. 2016;352:565-569.
5. Imhann F, Bonder MJ, Vich Vila A, et al. Proton pump inhibitors affect the gut microbiome. *Gut*. 2016;65:740-748.
6. Freedberg DE, Toussaint NC, Chen SP, et al. Proton pump inhibitors alter specific taxa in the human gastrointestinal microbiome: a crossover trial. *Gastroenterology*. 2015;149:883–885.e.9.
7. Bavishi C, Dupont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. *Aliment Pharmacol Ther*. 2011;34:1269-1281.
8. Tsai C-F, Chen M-H, Wang Y-P, et al. Proton pump inhibitors increase risk for hepatic encephalopathy in patients with cirrhosis in a population study. *Gastroenterology*. 2017;152:134-141.
9. Dultz G, Piiper A, Zeuzem S, Kronenberger B, Waidmann O. Proton pump inhibitor treatment is associated with the severity of liver disease and increased mortality in patients with cirrhosis. *Aliment Pharmacol Ther*. 2015;41:459-466.
10. Krag M, Marker S, Perner A, et al. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. *N Engl J Med*. 2018;379:2199-2208.

DOI: 10.1111/apt.15428

Editorial: HBV—the naked truth?

In a recent issue of AP&T, Jiang *et al*[1] described the characterisation of an envelope deletion variant of hepatitis B virus (HBV) isolated from a patient. The authors showed that the deleted amino acid domain 25-39 of PreS1 contributes to viral morphogenesis and affects hepatitis B surface antigen (HBsAg) secretion. However, what is the role of the deletion variant virus produced in the patient? It is well known that HBV particles contain a partially double stranded circular DNA encapsidated by 180-240 copies of the hepatitis B core antigen (HBcAg) covered by a lipid-bilayer outer shell containing three versions of the HBsAg (small, middle and large[2];). The large HBsAg (LHBsAg) is responsible for viral attachment and entry using the Na^+-taurocholate cotransporting polypeptide (NTCP) receptor on hepatocytes.[3] Antibodies to the three forms of HBsAg (SHBsAg, MHBsAg, LHBsAg) are the classical antibodies that ostensibly neutralise the viral particle. In contrast the dominant antibody response to HBV is, as with many viral infections, directed at the capsid protein hepatitis B core antigen (HBcAg). The antibodies to HBcAg, anti-HBc, are generally considered to have no biological effect during the infection as this antigen has not been identified on the surface of the virus or the infected cell. So, how may B cells come in contact with a subcellular antigen, apart from lysis, leakage or disruption of infected cells? The current paper showed that a mutant, patient-derived, HBV particle may not in all cases be completely covered by the envelope. In fact, a portion of HBV particles are partially naked, meaning that part of the viral exterior is actually HBcAg. The particles obviously appear *in vivo* but do not seem to be infectious, as the NTCP binding site within the PreS1 domain of the LHBsAg protein has been disrupted. This raises two questions: what is their role in infection and how is the deletion variant selected? This deletion variant was shown to be non-infectious: this would indeed be a detrimental deletion variant that should only be expressed from a defective cccDNA or an integrated gene fragment. The main question is, what are the implications of this finding? Is this merely an interesting epiphenomenon that is of no signficance or is there more to learn and discover about partially naked HBV particles? Theoretically, they should be rapidly"neutralized" and cleared by the existing circulating high levels of anti-HBc (Figure 1). In fact, the presence of the high levels of anti-HBc may even be amplified by the presence of partially enveloped HBV particles, as this would shuttle HBcAg to the antigen presentation pathway.[4] Is there any other functional significance of these particles? The authors propose that these particles may help

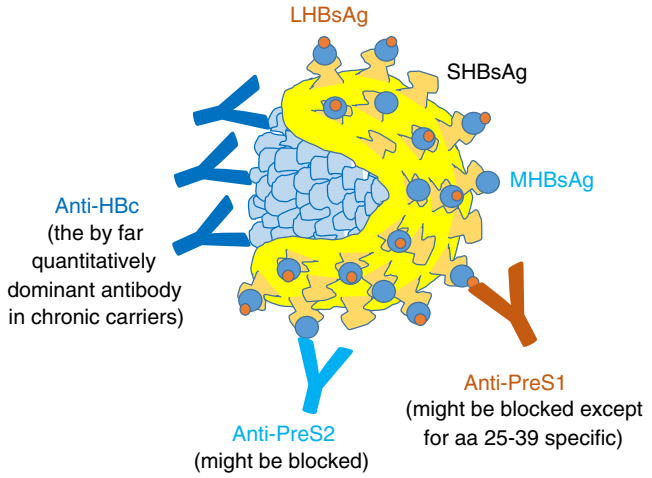

FIGURE 1 Schematic description of the possible function and limitations, of the preS1-deletion variant

to block PreS1 and PreS2 antibodies not affected by the deletion. However, this would require a substantial level of production of these particles. Finally, it is likely that the high levels of anti-HBc in the sera would rapidly clear these particles from the circulation, whereby their ability to block PreS1 and PreS2 antibodies may be limited. Or can these particles still bind PreS1 and PreS2 antibodies when bound by anti-HBc? In that case the anti-HBc response may help to clear PreS1 and PreS2 antibodies. The naked truth about these interesting newly observed *in vivo* partially enveloped and partially naked, HBV remains elusive and points to gaps in our understanding of hepatitis B replication and the looming complexity of potential cures.

ACKNOWLEDGEMENTS

All authors have contributed to the writing of the manuscript and have approved the final version.

Declaration of personal interests: MS is a co-founder and co-owner of Svenska Vaccinfabriken Produktion AB that hold patent applications related to HBV, HDV and cancer therapies.

LINKED CONTENT

This article is linked to Jiang et al papers. To view these articles, visit https://doi.org/10.1111/apt.15381 and https://doi.org/10.1111/apt.15452.

Anna Pasetto
Gustaf Ahlén
Matti Sällberg

Division of Clinical Microbiology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden
Email: matti.sallberg@ki.se

ORCID

Matti Sällberg https://orcid.org/0000-0002-8858-5132

REFERENCES

1. Jiang B, Wu Q, Kuhnhenn L, et al. Formation of semi-enveloped particles as a unique feature of a hepatitis B virus PreS1 deletion mutant. *Aliment Pharmacol Ther*. 2019;50:940-954.
2. Dryden KA, Wieland SF, Whitten-Bauer C, Gerin JL, Chisari FV, Yeager M. Native hepatitis B virions and capsids visualized by electron cryomicroscopy. *Mol Cell*. 2006;22:843-850.
3. 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.
4. Lazdina U, Alheim M, Nyström J, et al. Priming of cytotoxic T cell responses to exogenous hepatitis B virus core antigen is B cell dependent. *J Gen Virol*. 2003;84:139-146.

DOI: 10.1111/apt.15452

Editorial: HBV—the naked truth? Authors' reply

In their editorial, Pasetto et al comment on our new observation about the formation of semi-enveloped particles by a hepatitis B virus PreS1 deletion mutant.[1] They questioned the implications of this finding.[2] It is not merely an interesting epiphenomenon. Instead, it is of significance in virion assembly and development of antiviral strategies.

Stepwise repair of variant genome rescued the formation of intact fully enveloped viral particles and regular sized filaments, which shows the importance of the N-terminal part of the PreS1-domain (aa 25-39) for the properly assembled virions and filaments. It is in contrast to existing models claiming that the N-terminal PreS1 domain is dispensable for virion assembly.[3,4] Thus, these data define a new region required for HBV morphogenesis. They underline that morphogenesis of virions and of filaments share a variety of common features that differ from the morphogenesis of spheres. As both morphogenesis of virions (harbouring a nucleocapsid) and of filaments (lacking a nucleocapsid) is affected by deletion of this region, we conclude that this region triggers proper LHBs-assembly in virions and filaments independent of a direct interaction with the nucleocapsid.