

**COMPARTMENTALIZATION OF HEPATITIS B VIRUS:
LOOKING BEYOND THE LIVER**

Reviewed by 03384692

This invited editorial is a brief overview of a few recent papers discussing compartmentalization of hepatitis B virus. The "Text" section is adequate and reports on the findings of several other researchers, as well as the author's own research group. The "Conclusion" section could be expanded or reworked into the Text (see points below).

Suggested Changes

1. Consider including a primary reference for the opening statement regarding the hepatotropic nature of hepatitis B virus.

Done

2. Additional references should be added to the sentences following, regarding extrahepatic sites.

Done

3. There is an error in the text in this region, as it looks as if two sentences have been incorrectly joined into one.

Corrected

4. The author should remove the word "etc." from this section.

Removed

5. Avoid using the names of researchers within the manuscript text. This style has been used on several occasions ("Professor Michalak's research group", "Coffin and colleagues"). These sections should be reworded so that standard referencing is used, without the names of researchers in the text.

Corrected

6. The Conclusion is adequate, but could be strengthened by including a deeper synthesis of the preceding material.

Done

7. The word "seem" in the section ". . . the viruses seem to infect and persist . . ." should be changed.

Done

8. The word "Fascinatingly" should be replaced in both instances where it was used.

Done

9. Proof-reading by a native English speaker is required to correct small errors throughout the manuscript.

Done

10. The message of the paper is not communicated clearly to the reader. Consider expanding the Conclusion, or combining it with the main text and adding some additional synthesis.

Done

Reviewed by 02445121

In this editorial, the author provided an overview of the current evidence based information on the phenomenon of compartmentalization of HBV in the PBMCs, their clinical relevance in emergence of escape mutants/ drug resistant strains and also significance in transmission of infection through intrauterine routes. The author also discussed the knowledge gaps that need to be filled to properly understand the biological and clinical relevance of extrahepatic tropism of HBV. This editorial is described in detail, which, as valuable information, could help the readers that have better understand the first and knowledge of this topic to start novel studies.

I sincerely thank the reviewer for his/her appreciation of the article.

Reviewed by 01562153

Hepatitis B virus (HBV) is considered to be hepatotropic, but evidences demonstrate its extra hepatotropic nature. The evolution of HBV DNA occurs in extrahepatic compartments leading to the emergence and selection of escape variants or drug resistant strains, and, perhaps, being involved in the intrauterine transmission of HBV. In this manuscript, the author reviews the current knowledge on the compartmentalization of hepatitis B virus, and delineates the gaps that are required to understand the biological and clinical relevance of extrahepatic tropism of HBV. The originality of this manuscript is not high. However, this is an interesting article that elicits the attention to the extrahepatic compartments of HBV infection. Thus, this article may provide some useful information for the clinicians.

I sincerely thank the reviewer for his/her suggestions and comments.

Minor comment:

1. The author claims that HBV infected PBMCs from the mothers are able to infect the placental membrane, cross it and infect the fetus, and that the PBMC mediated vertical transmission of HBV is a frequent event. If it is the case, why the rate of intrauterine transmission is so low? Why the injection of hepatitis B immunoglobulin (HBIG) and HBV vaccination after birth can prevent the vertical infection of HBV? And why the administration of oral antiviral agent to HBV at the third trimester of pregnancy can prevent the vertical infection? The author should explain this discrepancy.

I wish to clarify here that the facts presented in this article have been adopted from peer reviewed published literature, primarily based on the findings of some recent studies presented in *Shao et al., 2013, Bai et al., 2011, Xu et l., 2015*. The reviewer has rightly pointed a very interesting and important aspect of extrahepatic HBV, which I would like to explain through following few lines.

The phenomenon of extrahepatic HBV infection (with special reference to PBMCs), is now understood to be markedly different from the HBV infection in serum/ liver, in terms of persistence and transmission. As discussed in the text also, *Xu and colleagues (2015)* have clearly demonstrated that mother to fetal PBMC traffic significantly increase the risk of PBMC HBV infection in newborns, while no noteworthy association was found between mothers to fetal PBMC transfer and serum HBsAg and/or HBV DNA

positivity in the newborns. It may simply be understood from these findings that PBMC mediated HBV infection remains restricted to the PBMCs of the newborns, hence it is not reflected as serum HBsAg or HBV DNA positivity. Similarly, the preventive action of HBIG and oral anti-virals, as mentioned by the reviewer is chiefly evaluated based on HBsAg/HBV DNA positivity in neonatal serum, but the PBMCs are seldom considered in such evaluations. I personally believe that, if PBMCs from infants born to PBMC HBV positive mothers (including those receiving therapy) are tested, a high frequency of HBV positivity could be registered, since PBMCs and HBV residing there have also been reported to be resistant to HBIG and antiviral therapy.

Through the present editorial, I wish to encourage such non-classical studies for better understanding of extrahepatic tropism of HBV, compartmentalized evolution and their transmission.

2. The woodchuck model is different from the HBV infection in human. So the author should not use the findings from woodchuck HBV study to implicate the situation in human HBV infection.

With my deepest regards to the reviewer, I wish to inform that the woodchuck hepatitis virus has long been recognized and used as a model for studying and understanding pathogenesis as well as therapeutic response, due to its remarkable similarities with human HBV infection. The following literature clearly attests to this fact.

- i) Menne S, Cote PJ. The woodchuck as an animal model for pathogenesis and therapy of chronic hepatitis B virus infection. *World J Gastroenterol*. 2007; 13: 104-124.
- ii) Tennant BC, Toshkov IA, Peek SF, Jacob JR, Menne S, Hornbuckle WE, Schinazi RD, Korba BE, Cote PJ, Gerin JL. Hepatocellular carcinoma in the woodchuck model of hepatitis B virus infection. *Gastroenterology*. 2004; 127: S283-S293.
- iii) Tennant BC, Gerin JL. The woodchuck model of hepatitis B virus infection. *ILAR J*. 2001; 42: 89-102.
- iv) Roggendorf M, Tolle TK. The Woodchuck: An Animal Model for Hepatitis B Virus Infection in Man. *Intervirology*. 1995; 38: 100-112.

Taking the above mentioned literature into consideration, I am in opinion that the findings of extrahepatic WHV infection and transmission might also be implicated in case of human HBV infection, as discussed in the present article.

3. The English of this manuscript needs polishing.

Done