

Dear Editors:

Name of journal: *World Journal of Virology*

ESPS Manuscript NO: 16352

thank you very much for considering our manuscript (ESPS manuscript number 16352, Molecular interactions between hepatitis B virus and Delta virus) for publication in World Journal of Virology. We greatly appreciate the insightful comments by the referees that indeed helped us to improve the manuscript.

In the revised version, we addressed all issues raised by the reviewers and included additional information. Specifically, we added new information to our figure as well as the text, addressing the molecular importance of HDV genotypes and L-HDAg C-terminal domain in HDV packaging process.

The changes in the revised version of our manuscript are underlined.

We hope you find our manuscript now suitable for publication in your journal. Please find our point-to-point responses to the referees' comments below.

Kindest regards,
Frank Tacke
University Hospital Aachen, Germany

Point to point responses

Reviewer #1: The manuscript of Shirvani-Dastgerdi and Tacke "Molecular interactions between hepatitis B virus and Delta virus" contains an excellent review, is well documented and interesting to read. However, it presents some minor limitations that must be resolved before possible publication:

1. 1-The authors should comment more broadly the important degree of HDV variability, especially in the C-terminal region of L-HDAg, which as they themselves indicate, is responsible for the interaction of this HDV protein with HBV envelope. They should include appropriate citations to confirm this variability (different until more than 70% between 8 genotypes VHD).

Response:

We thank the reviewer for this comment. To better highlight the importance of HDAg C-terminal region we added more data explaining the role of packaging signal residues in HDV envelopment and L-HDAg-HBsAg interactions. We also discuss the dissimilarity of disease severity caused by different genotypes of HDV. The added parts are underlined in the revised version.

2. Not quote or comments about HDV genotype classifications in 8 genotypes of HDV are included. These comment, must be included, in addition to some comment about if HDV

genotypes may be associated with differences in the interaction between HBV and HDV and even in the clinical behavior of this infection among different genotypes of both viruses

Response:

We sincerely thank the reviewer for this important comment. Since each genotype of HDV has a specific pattern of residues in L-HDAg C-terminal domain, describing the role of this domain will point to the association of HDV genotypes and different L-HDAg-HBsAg interactions. In our revised version, we have discussed both issues (the role of L-HDAg C-terminal domain and the importance of HDV genotypes). Moreover, different studies have suggested that there is no specific association between HDV and HBV genotypes, and the observed co-infection of the viruses (HDV-3/HBV-F or HDV-1/HBV-D) might be representative of the common genotypes in particular geographical areas. All these comments are included in the revised version.

3. On page 4 a reference to packaging signal in Figure 1 is made, however in this figure nothing of this signal is indicated. In the legend of Figure 1 it is included the acronym RNP: ribonucleoprotein, but in this Figure this term does not appear.

Response:

Thanks to the reviewer for pointing out this important issue. We have now added a highlighted zone to the spheres representing L-HDAg to indicate the packaging signal (C-terminal domain of L-HDAg). The ribonucleoprotein (RNP) complex of HDV is also shown in the revised figure.

Reviewer #2: No specific comments.