Dear editors,

Thank you very much for the positive evaluation of our review!

In the following please find our answers to the valuable comments of the reviewers. We integrated their recommendations as follows.

With kind regards

Stephanie Jung and Ulrike Protzer

2 Peer-review report

Reviewer #1: The article by Jung S et al, entitled "Innate Immune Recognition and Modulation in Hepatitis Delta Virus Infection", addresses the complicated and difficult subject of the immune response, or more precisely the lack of an immune response in HBV and HDV co-infection. From a virological and immunological point of view the article is very well written and easy to understand. Special mention should be also made of the two figures listed in the article and their concise note. The authors, and in particular the corresponding author, are well known for their research activity in virology and especially hepatitis B virus. However, clinically, the article needs improvement. One would expect more reference on issues concerning the natural progression of the acute and chronic HDV infection and its medical treatment. More specifically, I would like the authors to refer and answer questions such as: a. What is the immunological background of acute HBV-HDV co-infection? In that situation there is a strong, often excessively so, immune response usually leading to clearance of the infection and sometimes to death. What is the role of HDV as opposed to HBV? b. What is the immunological background of the frequent transition to chronicity of the acute HDV superinfection? c. What is the underlying immunological cause of the rapid evolution to cirrhosis and hepatic failure of patients with hepatitis delta? Since HDV stimulates the immune system very little, why is the evolvement of chronic delta infection rapid, even faster than the (simple) chronic HBV infection?

The first three questions have been addressed in the subchapter "introduction".

d. Authors could further emphasize the therapeutic antiviral activity of interferon at an immunological level, and provide possible explanations for why this beneficial effect is not observed in most patients. I believe that with improvements, as suggested above, the article will attract, among else, wider clinically oriented readership.

This question has been addressed in the subchapter "Immune evasion by HDV".

Reviewer #2: This is a wonderful review of Hepatitis Delta Infection (77 references) and is through and comprehensive. I really enjoyed reading the paper and it was very informative. I can't wait until it is published so I can share it with my colleagues. I have only once suggestion, which is to break up the four-line sentence at the bottom of the middle paragraph under the heading "Impact of HBV Coinfection" (page 6). I would write that sentence as follows: An inhibition of interferon responses by HBV, however, has also been described in mice with humanized livers. One would expect these livers to be close to the human physiological situation although HBV replication levels maybe higher due to the lack of adaptive immunity and a cross-talk between human hepatocytes and murine non-hepatocytes. This is just a suggestion but the sentence, as it stands now, is confusing and is definitely a run-on sentence. Otherwise the English is perfect, and I loved the paper

The sentence has been modified as recommended.

Reviewer #3: The review by U. Protzer's group describes current understanding of interplay between hepatitis delta virus (HDV) infection and innate immune response, and with viral RNA sensors in a host cell in particular. The title clearly shows the topic of the review. In the text the authors provide a brief but very informative background of HDV molecular biology and life cycle. Then it states which sensors are used by the virus, presents an overview of an influence of hepatitis B virus on interferon response, and discusses it basing on the data from various systems used in the field. Finally, the authors briefly present current understanding what is an impact of interferons on HDV infection. The text is very clearly and concisely written and is very informative. The review is citing all the key references in the field. So, in my understanding it can be published in the current form. At the same time I have three comments that are suggestions rather than requirements. 1. The authors always refer to type I interferons. It could be worth mentioning that HDV can trigger production of type III interferons as well by the same PRR. Actually, the reference 24 contains this data.

This issue has been complemented in subchapter "Pattern recognition to HDV".

2. While discussing HDAg overexpression and activation of the NFkB factor, it could be mentioned that protein overexpression can lead to ER Overload Response (EOR) (see R. Kaufman's reviews) that does result in NFkB activation. It could serve as a nice speculation to the assumption that the effect could be due to simple overexpression of HDAg.

This point has been included in the part "sensitivity of HDV to antiviral Cytokines".

3. I may have missed discussion if HDV does (or does not) induce IFN production in patients. Actually, I am not aware if such data exist. But in any case existence/absence of such data could be mentioned.

Unfortunately, we are also not aware of these data. As recommended, we now mention this in the chapter "immune evasion by HDV".

Reviewer #4: This review study is well written and well organized. In this study, the authors have demonstrated what is known up-to-date about the innate immune recognition and modulation in HDV infection as well as the interplay between HBV and HDV's immune evasion strategy. Although, there are many unknown remains in this regards. Generally, this is an informative and valuable review study.