

Dear editor,

Thank you very much for your encouraging letter together with the reviewers' constructive suggestions regarding our review entitled "**Role of Tim-3 in hepatitis B virus infection: An overview**". As you suggested, the manuscript has been revised according to the comments and suggestions of reviewers and the editor, and we have responded, point by point, to the comments as listed below. All the changes have been highlighted in the revised manuscript. We believe the revised manuscript has satisfied the concerns that were raised and therefore hope it is acceptable for publication in *World Journal of Gastroenterology*.

If you have additional questions or need further clarification, please contact with me. I am looking forward to hearing from you.

Yours sincerely,

Chunhong Ma

Reviewer No. 2448976:

- 1. When discussing the various ligands for Tim-3, it is important to discuss Tim-3 regulation by CEACAM1 (Nature 2015), which the authors failed to mention.**

Thanks for the kind suggestion. In the revised manuscript, we included information about CEACAM1 (page 7, paragraph 1).

- 2. Please provide the reference for "Blockage of Tim-3 with neutralizing Ab, anti-viral immune response was rescued to a certain extent"**

As suggested, reference was added as [15] (page 8, paragraph 2).

- 3. Mention of Figure 1 is only given in the conclusion: Why not mention it earlier in relation to the various statement in the text?**

Thanks for your suggestion. Figure 1 is now mentioned at the end of the first and second section besides conclusion part (page 12, paragraph 3 and page 16, paragraph 3).

- 4. Under "Tim-3 and innate immune response in HBV infection" The authors wrote, "A large body of evidence has proved that Tim-3 also regulates innate immune response." This statement needs to be substantiated in more details and not left as a blanket statement.**

As suggested, we substantiated the statement as following "Unlike adaptive T cells, innate immune cells such as monocytes/macrophages, NKs and NK T cells

(NKTs) constitutively express Tim-3, which can be further elevated in some diseases including chronic viral infection. Interference of Tim-3 pathway changes the function of innate immune cells” (page12, paragraph4)

- 5. Page 12: In the description of the response of monocyte/macrophages to TLR activation there seems to be some statements unrelated to the actual review topic: The sentences “it seems to benefit for the phagocytosis capacity of macrophages as a receptor recognizing. Blockage of Tim-3 leads to accumulated apoptotic bodies at the uteroplacental interface[46].Tim-3 seems to be responsible for the recognition and presentation of dying cell-related antigen[47].” Make no sense or relation in my mind and that needs to be either modified or taken out.**

Thanks for your suggestion. The statement about Tim-3 mediated phagocytosis of apoptotic cells of macrophages was deleted from the revised manuscript.

- 6. There are also many typos, grammatical errors and poor choices of words, throughout the manuscript, review by a native English speaker is absolutely needed.**

As suggested, a native English speaker from (Nature Publishing Group Language Editing) help us revise the language.

Review No.3021397:

- 1. Figure 1 is in the section of conclusions and prospects, to the end of the text. It would be more useful to describe it in the first sections.**

Thanks for your suggestion. Figure 1 is now mentioned at the end of the first and second section besides conclusion part (page 12, paragraph 3 and page 16, paragraph 3).

- 2. There is an abuse of the term “besides”, it is suggested replace with synonyms. Minor spell check required.**

As suggested, all synonyms and spell have been carefully checked in the revised manuscript. Also, the revised manuscript has been got language certificate by professional English language editing company (Nature Publishing Group Language Editing).