ANSWERING REVIEWERS

January 19, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 15481-review.doc).

Title: Hepatitis C virus and antiviral innate immunity: who wins at tug-of-war

Author: Darong Yang and Haizhen Zhu

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 15481

The manuscript has been revised according to the suggestions of the editor and the reviewers:
1 Format has been updated and we believe that the language of the manuscript has reached grade A.

2 Revision has been made according to the suggestions of the reviewer.

(1) Reply to reviewer # 02992723:
We sincerely appreciated the reviewer for the comments.

(2) Reply to reviewer # 02957000:
Comments:
a) This review is comprehensive and well written. I have some issues that need to be addressed: In the abstract it is stated that "However, HCV has also acquired numerous strategies, including viral factors and host genetic factors, to escape host immune response that facilitates viral persistence." HCV does not acquire host genetic factors per se but may develop immune evasion strategies or modulate the immune response. The sentence should be rephrased. In the Introduction the fourth sentence states "As the virus replicates....". The sentence should be rephrased e.g by removing the initial word "As".
Responses:
We appreciated the reviewer for the comments. We have rephrased the sentences according to the reviewer's suggestions.

Comments:
b) As the authors state DAAs has been introduced to the market as new successful treatment options. PegIFN-α plus ribavirin is listed as the current standard-of-care, but this is not the case in many centers where DAAs is being increasingly used. The authors should instead write, that although DAAs recently have been introduced, PegIFN-α is still the current standard-of-care in many treatment centers. This also applies for the "Conclusion" section.
Responses:
Following the reviewer's suggestion, we have corrected the description of DAAs in the sections of "Introduction" and "Conclusion".

Comments:
c) At the last part of the section "The life cycle of HCV" the authors briefly mention their own work

using a SELEX-method to screen a series of specific aptamers targeting viral proteins Core. The authors should elaborate on how their own research relates to the life cycle of HCV. It is not sufficient just to state that some aptamers have been screened and that they may hold promise for further investigation.
Responses:
Thanks the reviewer for the comments. The detailed mechanisms underlying how HCV protein- specific aptamers affect the life cycle of HCV were added in the revised manuscript.

Comments:
d) In the section "Models for HCV infection" the authors give an overview of cell culture models and animal models for studying HCV. Both sub-sections are interesting, but they do not integrate well with the remaining part of the manuscript. Although the reader is being introduced to different HCV models, this knowledge is only very few times made relevant to the reader when going through the literature in the remaining part of the manuscript. Unless the authors are able to draw more clear lines from the different HCV models to the other sections of the manuscript, I have to recommend, that the part about models for HCV infection is removed.
Responses:
Following the reviewer's suggestions, we have improved the logic relationship between the "Models for HCV infection" section and the remaining part of the manuscript.

Comments:
e) Table 1: The table including legend should be self-explanatory. The legend needs to be extended to explain the content of the table.
Responses:
Thanks the reviewer for the suggestion. The content of legend was extended for better description of "Table 1" in the revised manuscript.

(3) Reply to reviewer # 00398239:
Comments:
a) The authors summarized recent advances in the studies of the innate immune response to HCV infection and viral escape of the innate immune system. This review is well written; however, I am afraid that the authors did not describe some of important recent studies as described below. Comment 1: I am afraid that the description of the role of TLRs in sensing HCV RNA is not sufficient. Dreux M et al (Cell Host & Microbe 2012, 12(4): 558-570) reported that HCV RNA-containing exosomes were transferred from infected hepatocytes to pDCs, leading to TLR7-dependent type I IFN production from pDCs. There are several other reports describing exosome-mediated HCV RNA transfer. The authors should describe the exosome-mediated transfer of HCV RNAs from infected cells to DCs, leading to the TLRs activation.
Responses:
We appreciated the reviewer's comments. The role of exosomes in transmitting of HCV RNA and TLR7-dependent innate immune response was systematically reviewed in the section of "Toll-like receptors sense HCV".

Comments:
b) Comment 2: The authors described the RIG-I and its regulatory factors, such as TRIM25 and unanchored polyubiquitin chain. I am afraid that their explanation is not clear. Previous studies have revealed that RIG-I activation is initiated upon biding of PAMP RNA, leading to K63-linked polyubiquitination (or association with K63-Ub chain) and association with 14-3-3epsilon (Ref. 102). The authors also reported a ubiquitin ligase TRIM25 as a ubiquitin ligase that activates RIG-I. But, recent studies revealed that other two ubiquitin ligases, Mex3c and Riplet, are also essential for K63-linked polyubiquitination of RIG-I (Kuniyoshi K et al PNAS 2014: 111(15):5646-5651, Oshiumi H et al PLoS Pathog. 2013, 9(8): e1003533). The authors should improve the description of RIG-I activation

and modification steps.

Responses:

Thanks the reviewer for the suggestions. We have improved the section of "RIG-I-like receptors detection of HCV" by adding of the recent discoveries of E3 ubiquitin ligase Mex3c and Riplet as well as unanchored polyubiquitin chain relating to activation of RIG-I signaling.

Comments:

c) Comment 3: Relate to comment 2, a recent study indicated that the Riplet ubiquitin ligase, that is essential for RIG-I activation, is cleaved by HCV NS3-4A (Oshiumi H et al PLoS Pathog. 2013, 9(8): e1003533). The authors should describe NS3-4A-mediated cleavage of Riplet.

Responses:

Indeed, NS3/4A-mediated cleavage of Riplet is a novel mechanism for HCV evasion of antiviral innate immunity. The revised manuscript has covered this aspect in the section of "Viral factors".

(4) Reply to reviewer # 02916928:

Comments:

Yang and Zhu reviewed the molecular mechanisms of how the intracellular innate immune system detects HCV infection and the role of immune effectors to restrict HCV. Moreover, the article emphasizes the key innate immune evasion strategies used by HCV to establish chronic infection, as well as the influence of host genetic factors on the outcome of HCV infection and response to interferon-based therapies. The manuscript is well-organized, the literature review is thorough, and the data is interpreted adequately. The Table and Figures are helpful to the reader.

Responses:

We sincerely appreciated the reviewer for the comments.

3 References and typesetting were corrected.

Once again, we sincerely thank the editor and reviewers for your efforts to improve the quality of the revised manuscript submitted to the *World Journal of Gastroenterology*. We would be glad if the revised manuscript would give you complete satisfaction.

Sincerely yours,

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