ANSWERING REVIEWERS

December 6th 2013

Dear Editor,

Please find enclosed the edited manuscript in word format (file name 5901-review.doc).

Title: Understanding the interaction of hepatitis C virus with host DEAD-box RNA helicases and the involvement of these helicases in the pathogenesis of hepatitis C and hepatocellular carcinoma

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5901

The manuscript has been improved according to the suggestions of the reviewers:

1. Revisions have been made according to specific suggestions provided by Reviewer 2, Reviewer 3 & Reviewer 4

Reviewer 2

1) Introduction: References are required to support the author's statement, i.e. "According to statistics by the World Health Organization (WHO), about 150 million people (or 3% of the world's population) are chronically infected with hepatitis C; an estimated 3-4 million new infections emerge every year and hepatitis C-related diseases claims the lives of more than 350,000 people yearly." and "Recently, some DEAD-box RNA helicases have also been shown to be involved in the progression of several types of tumours including HCC."

Response: For the first instance, a new reference has been included to corroborate the HCV-related statistics (Reference 1). References for the second instance have been

provided later in the manuscript in the section titled "DEAD-box proteins and liver cancer" and have also been included in Table1.

2) Page 5, 7th line from the bottom: "However, the efficacy of these new drugs is not genotypewide, and several infected individuals respond poorly." I suggest to change "several" to "some".

Response: This revision has been implemented

3) Page 7, 1st and 2nd lines from the bottom: "…including entry, replication, assembly and release, to be studied in hepatoma cell lines. As described below, this has allowed much progress to be made in the characterization of…" change to "…including entry, replication, assembly and release, based on the studies in hepatoma cell lines. As described below, this has allowed much progress that had been made in the characterization of…"

Response: The sentence has been modified to ensure better clarity.

4) Page 16, 2nd line of the last paragraph: "ribonucleoproteincomplexes" change to "ribonucleoprotein complexes".

Response: This revision has been implemented

5) Page 20, 1st line: "define the role viral-host interactions in HCV-induced pathogenesis." change to "define the role of viral-host interactions in HCV-induced pathogenesis."

Response: This revision has been implemented

6) Page 20, 9th line: “HCV induced human immune response, liver infiltration, hepatitis, and fibrosis[98].” What does liver infiltration mean? I cannot understand it.

Response: We acknowledge this error. The word “infiltration” has been changed to “inflammation”.

7) Table 1, Line of “DDX5”: “This study” What’s the meaning of these 2 words in the Reference column? I suggest deleting these 2 words to maintain consistence of this table.

Response: The words "This study" has been changed to "data presented herein".

Reviewer 3

1) Line 8, Page 16: Please capitalize the letter W for Western blot.

Response: This revision has been implemented

2) Page 19 and beyond: Please delete “as summarized in” throughout the manuscript.

Response: This revision has been implemented

3) Line 8, page 19: “in regulation HCV replication” should be “in regulation of HCV replication” or “in regulating HCV replication”.

Response: This revision has been implemented

Reviewer 4

1) Figures have to be accompanied with their legends. Cited data (Fig. 2 and Table 2) should be indicated properly

Response: Figure legends have been provided in a separate file from the figures as per the journal specifications. Cited data for Figure 2 has been referenced in parenthesis with superscript in compliance with the journal specifications. Cited data for Table 2 has been included in the table itself.

2) The original data (Fig. 3) should be accompanied with the methodology.

Response: A brief methodology has been provided in the figure legend. Since this is a review paper, the materials and methods were not included in the main text.

3) p. 3, l. 20; "Unlike…" This sentence should be deleted because it sounds too literary.

Response: The word "unlike" has been replaced with "Contrary to"

4) p. 4, l. 2; "HCV has a 9.6 kilo base pair genome…" HCV has single stranded RNA genome.

Response: This revision has been implemented

2. Content was modified according to suggestions made by reviewer 1 and reviewer 3

Reviewer 1

1) The description in the abstract could be more specific. Major DDXs implicated in HCV replication should be spelt out.

Response: This revision has been implemented in the abstract

2) It might be helpful to cite major reviews in HCV pathogenesis, carcinogenesis and treatment (e.g. Nature Medicine 19:837-849; Oncogene 30:1969-1983; Frontiers in Bioscience 12:222-233).

Response: Oncogene 30:1969-1983 had previously been cited already (Reference no 69). Nature Medicine 19:837-849 and Frontiers in Bioscience 12:222-233 have been included in the citations (Reference no 11 & 82 respectively).

3) RIG-I-like receptors including RIG-I, MDA5 and LGP2 are also DEAD-box RNA helicases. Their roles in HCV infection and pathogenesis should be briefly discussed.

Response: A new paragraph and relevant references have been added to the section titled "DEAD-box RNA helicases" (P7)

4) The suggested roles of DDX3 in innate antiviral immunity (e.g. in adapting IKK? to IRF3) should be discussed further in relation to HCV infection and pathogenesis.

Response: A brief summary outlining the role of DDX3 in innate antiviral immunity in relation to HCV infection and pathogenesis has been included in the section titled "DDX3 and HCV" (P8, first paragraph)

5) DDXs might have stage-specific roles in the initiation and maintenance of HCV infection and cancer. For example, they could play different roles in acute and chronic infection. It will be helpful to elaborate more on these ideas.

Response: We have expanded the last paragraph in the section titled "Conclusion and Future Perspectives" to elaborate on these ideas (P15-16).

Reviewer 3

1) Title: In the present manuscript, authors highlighted roles of host DEAD-box RNA helicases in pathogenesis of hepatitis C and hepatocellular carcinoma (HCC), that was not reflected concisely and fully in the present title.

Response: As per the reviewer's suggestion, the title has been modified to reflect the content of the study as best as possible.

2) HCV Genome and Viral Protein, Line 5, Page 4: HCV p7 protein is likely to play a role in HCV infection. Please include this protein in HCV Genome and Viral Protein.

Response: The p7 protein has already been included in the HCV genome and Viral Protein section of the manuscript. Since this section describes the virus structure and genotype, we have not elaborated on the functional aspect of the HCV proteins.

3) Concluding Remarks and Future Perspectives, Page 20 regarding small animal models for HCV research. Most recently, Dorner et al (Nature 2013) has reported a breakthrough and milestone in development of a genetically humanized mouse model for HCV research, in which the entire HCV life cycle can be completed and immune system is fully functioning. This genetically humanized mouse model will allow researchers to gain new insights into not only an important biology of HCV, pathogenesis of hepatitis C, but also carcinogenesis of HCC caused by HCV.

Response: The above-mentioned reference suggested by the reviewer has been included in the section titled "Concluding remarks and Future perspectives" (P15, last paragraph).

3. References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*

Sincerely yours,

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