RESPONSE TO REVIEWERS

July 30, 2013

Dear Dr. Ma,

Please find enclosed the edited manuscript in Word format (file name: 4322-review.doc).

Title: Hepatitis C Virus infection, microRNA and Liver Disease Progression

Author: Shubham Shrivastava, Anupam Mukherjee, Ratna B Ray

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 4322

1. We updated the format based on the reviewers' suggestion and journal's requirement.

2. We thank the reviewers for helpful criticisms in improving our manuscript. Our point-by-point response to the comments is provided below:

Reviewer 1:

We thank the reviewer for constructive criticisms in improving our manuscript. Our response to the comments is provided below:

1. In the Introduction of miRNA synthesis (Page 3), it is critical to discuss how miRNAs are transcribed and their transcription regulation.

Response: Based on the reviewer's suggestion, we have elaborated the miRNA mediated gene regulation section in introduction (Page 3, last paragraph).

2. In discussing the role of miRNAs in HCV replication, a table or schematic illustration that summarizes which miRNAs act on what step of HCV life cycle will be very helpful for readers.

Response: The reviewer made an important point here, and we have included a table summarizing the role of miRNA in HCV life cycle and in liver disease progression (Table 1).

3. For the Section 5 (Role of miRNAs in HCV-related HCC), it is crucial to elucidate how HCC develops in HCV-infected liver, and how miRNAs affect various pathways of carcinogenesis. However, this short paragraph insufficiently covers these major concerns.

Response: We have explained in detail how HCV viral proteins may play a crucial role in progression towards HCC (Page 7, first paragraph).

4. Section 7: miRNAs as therapeutics in HCV infection: The clinical trial of miravirsen is very promising, and this is the only miRNA-based therapeutics moved from laboratory to bench. The question remains whether this therapy will be the adjuvant or a replacement to current HCV therapeutics, such as protease inhibitors.

Response: There are several anti-HCV drugs are in clinical trial based on host factors which assist in viral replication such as, cyclophilin A. cyclophilin A inhibitors have shown to be effective in combination therapy with PEG-IFN/RBV highlighting the role of additional anti-HCV drugs in standard treatment. Anti-miR-122 therapy needs to be evaluated together with current HCV therapeutics to have better understanding of miRNA based therapy. Based on the reviewer's comment, we elaborated the exploitation of miRNA as anti-HCV drugs and consequences (Page 9, first paragraph).

Reviewer 2:

This review article clearly and concisely reviewed the recent progress on the roles of miRNAs in HCV life cycle and HCV-mediated liver disease progression. Moreover, the authors pointed the potentials of miRNAs as diagnosis, prognosis, and target tools for therapeutic modulation. This manuscript was well-written and its scientific contents and accuracy should be highly-ranked. Taken together, I recommend this article be published without further modification in 'WJH'.

We thank the reviewer for appreciation of our manuscript.

Reviewer 3:

We thank the reviewer for helpful suggestions in improving the manuscript. Our point-by-point response to the comments is provided below:

1. For the Introduction section: 1.1. It is suggested to emphasize on the fact that one miRNA has the ability to target many different sites on the same mRNA or on many different mRNAs. Consequently, a single miRNA can regulate the expression of many mRNAs and affect several cellular pathways. These concepts are vital when one consider the potential safety issues involved in modulation of miRNAs levels.

Response: We explained about combinatorial effect of miRNA and their effect on cellular pathways and the potential safety issues regarding miRNA as therapeutics (Page 3, last paragraph, Page 9, first paragraph).

1.2. It would be interesting for readers if miRNA biogenesis (and the main regulatory mechanisms controlling their expression) could be better characterized (a figure is suggested for that).

Response: Based on the reviewer's suggestion, we have elaborated the mechanism involved in miRNA mediated gene regulation (Page 3, last paragraph).

2. For the sake of clarity, it would be advisable to insert a table to sum up which miRNAs have been involved in each aspect of HCV chronic infection discussed throughout the manuscript (HCV viral replication, interferon response, inflammation and fibrosis, etc.).

Response: We have included a table summarizing the role of miRNA in HCV life cycle and their involvement in liver disease progression (Table 1), based on the reviewer's suggestion.

3. The relationship between miRNAs and liver cancer has been increasingly recognized (HCC risk, differentiation, biological behavior, response to chemotherapy, anti-miRNAs as therapeutic tools etc.) and this issue should be further developed by the authors.

Response: We have elaborated the role of HCV viral proteins in HCC development (Page 7, first paragraph) as well as potential of miRNA as anti-HCV drugs and its consequences (Page 9, first paragraph), as the reviewer suggested.

3. References and typesetting were corrected

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

Sincerely yours,

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