

## Format for ANSWERING REVIEWERS



March 28, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 9001-review.doc).

**Title:** Complex interactions between microRNAs and Hepatitis B/C viruses

**Author:** Hongxia Fan, Hua Tang

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 9001

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

1 Format has been updated

We have revised our manuscript according to the standards and format of World Journal of Gastroenterology.

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

(1) Response to reviewers' comments (reviewer: 00504271)

The manuscript by Fan and Tan which describes miRNA effect on HBV and HCV infection and HCC progression comprehensively is a good review. It is advised that the effect of miRNA on them and the expression of miRNA by their infection will be summarized in tables.

**Thanks for your suggestions. With the suggestions of the other two reviewers, we have summarized the effect of miRNA on HBV/HCV infection and the effect of HBV/HCV infection on miRNA expression and their functions in three figures, please figure 1, figure 2 and figure 3.**

It is also advised to draw a figure of HBx as the main actor and surrounded by miRNA for developing HCC.

**Thanks for your advice. According to your suggestion and the other two reviewers' suggestions, we have drawn a figure which summarizes the altered miRNAs in HBV or HCV infected patients and their contributions to the development of HCC. Please see figure 3.**

"miRNAs as prognostic markers in HBV- or HCV-related disease" section (p. 20) should be described as precisely as other sections.

**Thank you for your suggestions. We have added the related findings to complete this section.**

Minor points: The latest statistics should be used. See. WHO ([http://globocan.iarc.fr/Pages/fact\\_sheets\\_cancer.aspx](http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx)).

**Thanks. We have cited the latest statistics in our manuscript. "Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related death worldwide" has been changed to "Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second leading cause of cancer-related death worldwide". Please see the first two sentences in "Introduction" section.**

p. 11, l. 20; Although the original authors describe that "hepatitis infection," hepatitis-positive should be hepatitis B or C virus- positive.

**We are sorry for the mistake. "hepatitis-positive" has been changed to "hepatitis B or C virus-positive". Thank you.**

(2) Response to reviewers' comments (reviewer: 01557562)

Major comments; In this study, authors tried to review microRNAs associated with hepatitis B/C

viruses. Overall, this manuscript is well written. However, this manuscript is considerable rambling. Authors should summarize the reported microRNAs in some Tables.

**Thanks for your suggestions. According to the suggestions from you and the other two reviewers, we have summarized the reported microRNAs in three figures and one table. Please see figure1, figure 2, figure 3, and table 1.**

Moreover, this manuscript lacks new reports concerning microRNA related HBV or HCV infection and diseases because most cited reports were published by first half year of 2013.

**We have added the latest findings in our revised manuscript, please see reference 48,71,78,80,82, 110,111,119,129,130,133,144,147. Thank you.**

Minor comments; 1.If possible, authors should mention about microRNAs in chronic hepatitis from lifestyle-related diseases due to the recent increase in patients with hepatitis.

**Thanks for your suggestions. Your suggestion is reasonable. But considering that our manuscript is mainly focusing on the interaction between microRNA and HBV/HCV virus, we think it is better to not mention them.**

2.Concerning the first microRNA-targeted drug working by inhibiting miR-122, as stated in this review, satisfactory results have come up in clinical trials, but there remain some issues to be considered. In some previous reports, the treatment effect of interferon was associated with in vitro, decrease in the expression level of miR-122. However, in other reports, and it was conflicting results in the evaluation of clinical specimens. If needed, authors should consider them and mention in this manuscript. I will show the related papers as follows. Interferon modulation of cellular micro RNAs as an antiviral mechanism. Irene M. Pedersen Nature 449, 919-922 (18 October 2007) , Decreased levels of microRNA miR-122 in individuals with hepatitis C responding poorly to interferon therapy. Sarasin-Filipowicz M Nat Med. 2009 Jan;15(1):31-3 Biochemical and Biophysical research communications volume 438,issue1,16 August 2013

**Thanks for your suggestions. We have discussed them in the “Role of miRNAs in HCV expression and replication” section. Please see page 8.**

(3) Response to reviewers' comments (reviewer: 00058405)

In general, the review is very well written and complete. It reports the main studies on microRNA in viral hepatitis and hepatocellular carcinoma. However, I have some suggestions to improve the comprehension and to ease the readability of the review: 1) At the end of each section, I suggest the authors to include a table with the main articles on microRNA and their results.

**Thanks for your suggestions. According to the suggestions from you and the other two reviewers, we have summarized the reported microRNAs in three figures and one table. Please see figure1, figure 2, figure 3, and table 1.**

2) I suggest the authors to include two figures with the potential molecular mechanisms of microRNA in viral replication and tumorigeneis considering HBV and HCC infections.

**Thanks for your suggestions. We have drawn two figures to summarize the potential molecular mechanisms of microRNA in viral replication considering HBV and HCC infections. And one figures to summarize the potential molecular mechanisms of microRNA in tumorigeneis considering HBV and HCC infections. Please see figure 1, figure 2, and figure 3.**

3) A list of abbreviations should also be included to help the reader.

**We have added a list of abbreviations before the ‘abstract’ section. Thank you.**

4) The limitations and advantages to use microRNA in clinical practice should also be better discussed in the concluding remarks section. Some comments on cost-effectiveness of microRNA measurements would be of interest.

**Thanks for your suggestions. The discussion on the limitations and advantages of application of microRNA in clinic has been added in the “concluding” section.**

3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in dark ink, appearing to read 'Hua Tang', is shown within a rectangular frame. The signature is fluid and cursive, with a long horizontal stroke extending from the end.

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