

November 13, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5971-review.doc).

**Title:** Cellular reprogramming and hepatocellular carcinoma development

**Author:** Yun-Wen Zheng, Yun-Zhong Nie, Hideki Taniguchi

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

**ESPS Manuscript NO:** 5971

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

1 Format has been updated.

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

(1) From reviewer1, Reprogramming is one of the probable reasons of generating CSC in HCC, while dedifferentiation may also lead to stemness property of cells. Please refer to a review from Chris Jopling, et al. Nature, 2011.

Response: According to this helpful comment, we have cited the reference and complemented the description of the cell-dedifferentiation in stemness property gain.

(2) From reviewer1, The section "CELLULAR EPROGRAMMING OF HCC" would be stronger if a recapitulative schematic was added. And from reviewer2, I'd like to suggest to come up with a diagram for a brief summary of all possible reprogramming factors for HCC development.

Response: As your suggestion, we have designed a recapitulative schematic in revised manuscript as Figure 1.

(3) From reviewer2, the authors may want to make supplements to the setting of HCV infection in regard to the oncogenesis, as in the case of HBV they have mentioned in the manuscript.

Response: Thanks for your comments. The oncogenesis related to the HCV infection has been added in the revised manuscript as well as the case of HBV.

(4) From reviewer2, As it appears in the text, the authors give separate headings to elucidate the contents. However, to the reviewer the headings may look confusing as 'reprogramming' has been used for several times with no clear distinguishment from each other. Please make these more clearly separable.

Response: Thanks for your comments. Some of the headings as reprogramming were removed or replaced with more suitable words.

(5) From reviewer3, My only criticism concerns the fact that the authors take it for granted that all the HCC have a stem cell component. In fact, data from mice models of targeted oncogenesis actually show that HCC can also emerge from mature hepatocytes.

Response: We have noted the report on the mentioned. Although we describe that carcinogenesis as well as cancer stem cell development is involved in reprogramming, we never deny that non-stem cell mediated HCC and direct conversion or trans-differentiation exist in cancer formation. For complement as well as reviewer's opinion, we have added some restriction in summary.

3 References and typesetting were corrected.

From editor: Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.

PMID (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>)

DOI (<http://www.crossref.org/SimpleTextQuery/>). The format of all references should like "2" .

Response: we have revised all according to the suggestion.

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

Sincerely yours,



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