

World Journal of Gastroenterology

Science Editor, Editorial Office

Ze-Mao Gong

Re: Ms: No. 34172

Dear Dr. Ze-Mao Gong,

Thank you for considering our manuscript for publication and providing us with useful comments and helpful advice to improve the review. We have made revisions, in accordance with Reviewers' comments, which are shown **highlighted**.

Below we include a list of our responses to the Reviewers' comments.

We hope the manuscript is now acceptable for publication in World Journal of Gastroenterology.

Yours sincerely,

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Responses to comments

Review Number Id 02861363

1. This manuscript is very well written review paper and it contains a broad knowledge of not only HCC related cancer stem cells but also general stem cells. Since, the manuscript is not well focusing on the topic of the title, it might be difficult to understand the author's discussions and conclusions.

Response

We have changed de title in order to better fit the focus of the manuscript (page 1).

2. If authors can provide an additional figure that contains makers or pathways of hepatic cancer stem cells they described in the manuscript not by table, which would help readers to understand the paper more easily.

Response

We have provided such additional figure (figure 1), containing markers and pathways of hepatic cancer stem cells. Previous table 1 was kept as supplementary table 1 in order to provide references for each data included figure 1 (page 50).

3. Also figure 2 is too simple to explain this complicated situation. It requires to put more specific terms.

Response

We have included more specific terms and extended descriptions in such figure, now called figure 3 (page 52).

Review Number Id 02860871

This editorial entitled **“Are the progenitor cells the origin of liver cancer?”** by Flores-Téllez TNJ et al is interesting in its field. The authors analyzed that the cell of origin of HCC might be a progenitor cell and the conditions that are reported to induce cell stemness. This article is well written with few typos inside. Here are some comments:

Response

We have searched for typos and corrected them.

Major comments:

1. Author provide a clear schematic figure on the conditions that are reported to induce stemness and an integrated model of cancer cell of origin (CCO) and cancer stem cell (CSC) hypotheses in HCC. Although controversy about the exact definition of progenitor cell and cancer stem cell still remains and the concept is still evolving, in the paragraph, also in the figure and table, the author mainly discuss and use the term of cancer stem cell (CSC) instead of progenitor cell (LSPC) as the origin of liver cancer. Consider to revise the title of the article otherwise change the term.

Response

We have changed de title in order to better fit the focus of the manuscript (page 1).

2. Many sub titles are involved in the article, which are a bit messy, consider to use number and do not include subtitle which are not necessary linked to the main title.

Response

We have reviewed all subtitles: we eliminated those without relation to the main title and corrected some others. We also numerated all of them to improve clarity.

3. The subtitle in page 14 “Different phenotype but similar functionality” has not able to show with the references what the similar functionality are. It mainly discuss assays used to differ CSC and non SC.

Response

We change the subtitle for “Functional assays for the evaluation of different stem cells” in order to better fit the discussion (page 15)

4. In the figure 1, author explaining that stemness can be triggered by several stimuli including epigenetics, microenvironment, EMT and chemotherapy. It would be better each of these stimuli mentioned is explained clearly in the text. For instance, chemotherapy. Author did not explain exactly in the text what is chemotherapy influence on stemness.

Response

We have explained more in detail in the text each stimuli, including several examples for chemotherapy influence on stemness (pages 44-46).

5. In the figure, the author give question mark for different cells involved in adult liver regeneration, but not all cells. Provide explanation why hepatocytes has no question mark while other cells have.

Response

We remove the question marks and clarify in the figure legend that hepatocytes have the main role in adult liver regeneration (page 52).

6. Regarding your hypothesis that the origin of cancer cell in HCC is might be CSC, one study mention that the slow cycling cells in the HCC tumor were superior in colony formation, tumor initiation and resistance to anti cancer MPA as compared to fast-cycling cells. (“Differential Sensitivities of Fast- and Slow-cycling Cancer Cells to Inosine Monophosphate Dehydrogenase 2 Inhibition by Mycophenolic Acid”, *Mol Med.* 2015 Oct 13. doi: 10.2119/molmed.2015.00126). Please provide your opinion about this statement.

Response

We discussed such study in the text (page 9)

Minor comments:

1. In the page 8, the sub title is a bit contrived with a word “one marker”. It would be better to separate discussion between marker and the cell signaling.

Response

We separated the discussion between “markers” and “cell signaling”. Now the “cell signaling” section is under the new subtitle: “Main signaling pathways that govern the stemness” (pages 8-14).

2. In the first paragraph page 3, author wrote “In light of these complexities, it is not known whether the cause of the aggressive behavior of HCC is hepatic cancer stem cells (HCSCs) or.....” Please provide another possibility for comparison.

Response

We eliminated the phrase for clarity (page 3). HCSC role in HCC aggressive behavior is explained in the following sections.

3. In page 25 “According to the majority of previously described LSPC results...” has nothing to do with the sub title

Response

We agree, therefore we moved this section to a new one, under the subtitle “The dominant role of hepatocytes in hepatic regeneration” (pages 30-31).

4. The sub title “Relationship between liver regeneration and cell of origin of CSCs, The classical model of liver regeneration and Historical basis of oval cell/LSPC theory in rats” could be made into one bigger sub title. Also subsequent several sub title could be merged in one bigger topic/subtitle.

Response

We merged subtitles “The classical model of liver regeneration” and “Historical basis of oval cell/LSPC theory in rats” (page 20). We considered however that “Relationship between liver regeneration and cell

of origin of CSCs” is a different topic. We also eliminated/merged several subtitles in the subsequent sections (pages 21-29).

5. In page 45, provide reference for “It has been reported that pathophysiological changes in the liver during inflammation/regeneration could induce the initiation or promotion of liver cancers”

Response

We inserted the reference in the text (page 46).

6. Provide a table that summarize all possible studies mentioning progenitor cell / cancer stem cell as an origin of HCC

Response

We have integrated such table, as “Table 1” (page 51)

7. In the figure 2, it mentioned OCC however in the statement author mentioned CCO. Please stick to 1 term.

Response

We corrected the term for “CCO” (page 52).

Review Number Id 02860797

The author make a full efforts to thoroughly review this field and also provide some questions to be figured out in future research. This manuscript is very well organized. Only some typos exist.

Response

Thank you for your comments. We have searched for typos and corrected them.

Editor review

1. Please revise and perfect your manuscript according to peer-reviewers' comments.

Response

We have revised the manuscript accordingly.

2. Please provide language certificate letter by professional English language editing companies (Classification of manuscript language quality evaluation is B).

For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies mentioned in 'The Revision Policies of BPG for Article'.

Response

We have included an AJE language certificate.

3. You'd better offer us one paper with word format next (such as, .doc or .docx), which is easy to be edited and helpful to accept earlier. Thank you very much!

Response

We sent a .docx document this time.

4. Audio core tip:

In order to attract readers to read your full-text article, we request that the author make an audio file describing your final core tip, it is necessary for final acceptance. Please refer to Instruction to authors on our website or attached Format for detailed information.

Response

We have sent an audio core tip.

5. Please provide the decomposable figure of Figures, whose parts are movable and editable. So please put the original picture as ppt so that we can edit them easily.

Response

We sent the editable figures in .psd format from Adobe photoshop. We also sent the figures in .ppt format.

6. Please check that there are no repeated references!

Response

We have eliminated duplicated references.