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## PEER-REVIEW REPORT

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

**Manuscript NO:** 34172

**Title:** Are the progenitor cells the origin of liver cancer?

**Reviewer's code:** 02861363

**Reviewer's country:** Japan

**Science editor:** Ze-Mao Gong

**Date sent for review:** 2017-04-09

**Date reviewed:** 2017-04-16

| CLASSIFICATION   | LANGUAGE EVALUATION  | SCIENTIFIC MISCONDUCT                          | CONCLUSION   |
|--|--|--|--|
| <input type="checkbox"/> Grade A: Excellent            | <input checked="" type="checkbox"/> Grade A: Priority publishing     | Google Search:                                 | <input type="checkbox"/> Accept                        |
| <input checked="" type="checkbox"/> Grade B: Very good | <input type="checkbox"/> Grade B: Minor language polishing           | <input type="checkbox"/> The same title        | <input type="checkbox"/> High priority for publication |
| <input type="checkbox"/> Grade C: Good                 | <input type="checkbox"/> Grade C: A great deal of language polishing | <input type="checkbox"/> Duplicate publication | <input type="checkbox"/> Rejection                     |
| <input type="checkbox"/> Grade D: Fair                 | <input type="checkbox"/> Grade D: Rejected                           | <input checked="" type="checkbox"/> Plagiarism | <input checked="" type="checkbox"/> Minor revision     |
| <input type="checkbox"/> Grade E: Poor                 |  | <input checked="" type="checkbox"/> No         | <input type="checkbox"/> Major revision                |
|  |  | BPG Search:                                    |  |
|  |  | <input type="checkbox"/> The same title        |  |
|  |  | <input type="checkbox"/> Duplicate publication |  |
|  |  | <input type="checkbox"/> Plagiarism            |  |
|  |  | <input checked="" type="checkbox"/> No         |  |

### COMMENTS TO AUTHORS

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

## PEER-REVIEW REPORT

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

**Manuscript NO:** 34172

**Title:** Are the progenitor cells the origin of liver cancer?

**Reviewer's code:** 02860871

**Reviewer's country:** Indonesia

**Science editor:** Ze-Mao Gong

**Date sent for review:** 2017-04-09

**Date reviewed:** 2017-04-17

| CLASSIFICATION                                    | LANGUAGE EVALUATION   | SCIENTIFIC MISCONDUCT                          | CONCLUSION   |
|---|---|--|--|
| <input type="checkbox"/> Grade A: Excellent       | <input type="checkbox"/> Grade A: Priority publishing                 | Google Search:                                 | <input type="checkbox"/> Accept                        |
| <input type="checkbox"/> Grade B: Very good       | <input checked="" type="checkbox"/> Grade B: Minor language polishing | <input type="checkbox"/> The same title        | <input type="checkbox"/> High priority for publication |
| <input type="checkbox"/> Grade C: Good            |   | <input type="checkbox"/> Duplicate publication |  |
| <input checked="" type="checkbox"/> Grade D: Fair | <input type="checkbox"/> Grade C: A great deal of language polishing  | <input type="checkbox"/> Plagiarism            | <input type="checkbox"/> Rejection                     |
| <input type="checkbox"/> Grade E: Poor            | <input type="checkbox"/> Grade D: Rejected                            | <input checked="" type="checkbox"/> No         | <input type="checkbox"/> Minor revision                |
|   |   | BPG Search:                                    | <input checked="" type="checkbox"/> Major revision     |
|   |   | <input type="checkbox"/> The same title        |  |
|   |   | <input type="checkbox"/> Duplicate publication |  |
|   |   | <input type="checkbox"/> Plagiarism            |  |
|   |   | <input checked="" type="checkbox"/> No         |  |

### COMMENTS TO AUTHORS

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 : 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. 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. 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. 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. 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. 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. 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. 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. 3. In page 25 "According to the majority of previously described LSPC results..." has nothing to do with the sub title 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. 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" 6. Provide a table that summarize all possible studies mentioning progenitor cell / cancer stem cell as an origin of HCC 7. In the figure 2, it mentioned OCC however in the statement author mentioned CCO. Please stick to 1 term.



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## PEER-REVIEW REPORT

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

**Manuscript NO:** 34172

**Title:** Are the progenitor cells the origin of liver cancer?

**Reviewer's code:** 02860797

**Reviewer's country:** China

**Science editor:** Ze-Mao Gong

**Date sent for review:** 2017-04-09

**Date reviewed:** 2017-04-19

| CLASSIFICATION   | LANGUAGE EVALUATION  | SCIENTIFIC MISCONDUCT                          | CONCLUSION   |
|--|--|--|--|
| <input checked="" type="checkbox"/> Grade A: Excellent | <input checked="" type="checkbox"/> Grade A: Priority publishing     | Google Search:                                 | <input checked="" type="checkbox"/> Accept             |
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| <input type="checkbox"/> Grade E: Poor                 | <input type="checkbox"/> Grade D: Rejected                           | <input checked="" type="checkbox"/> No         | <input type="checkbox"/> Minor revision                |
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|  |  | <input checked="" type="checkbox"/> No         |  |

### COMMENTS TO AUTHORS

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.