

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Correlation between Amino Acid Metabolism and Self-renewal of Cancer Stem Cells: Perspectives in Cancer Therapy" (NO.: 74928, Review). The comments were extremely valuable and very helpful for revising and improving our paper. We have studied them carefully and have made point-to-point corrections, which we hope meet the criteria for approval. The revised portions are highlighted in yellow in the manuscript. In order to ensure accuracy and fluency of the language, we have re-edited the article language with the help of an English editing firm.

The main corrections in the paper and the responses to the reviewers' comments are as follows:

Responds to the reviewer's comments:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

Specific Comments to Authors: The authors made an extensive review about amino acids metabolism and cancer stem cells. Although the manuscript is well written, it becomes very exhaustive and turns into a long list of amino acids and their correlation with some embryonic stem cells, cancer stem cells and tumor properties. No real perspective into novel therapeutic approaches is presented in the manuscript

(thus the title does not really reflect the content of the manuscript), and other published articles have described similar data. There are inaccuracies about certain terms, such as the first sentence of the introduction which states: "Stem cells are pluripotent cells with...". However, most of stem cells are not pluripotent. Pluripotency characterizes embryonic (carcinoma) stem cells and iPSC, mostly. In my opinion, the manuscript does present enough originality to be published in its actual state.

Response:

We thank the reviewer for the positive comments and professional opinions about our manuscript. Your comments indeed provide a good direction for our text and drive our manuscript towards completion. We have modified and revised text accordingly.

Indeed, we did make a mistake while defining stem cells. We are aware that according to the differentiative potential, stem cells can be divided into three categories: totipotent, pluripotent, and unipotent stem cells^[1], of which, pluripotent stem cells mainly refer to embryonic stem cells and induced pluripotent stem cells^[2]. We wrote the definition as such because we wanted to pave the way for the proposal of cancer stem cells, but we probably did not use the best set of words to express the same. We apologize for the same. In order to highlight the importance of cancer stem cells and to improve the accuracy of the article, we have removed the definition of stem cells from the introduction. However, we still thank the reviewer for the reminder and will be more cautious with our writing in the future.

Secondly, in order to propose the potential mechanism and possibility of cancer therapy, we used "Correlation between Amino Acid Metabolism and Self-renewal of Cancer Stem Cells: Perspectives in Cancer Therapy" as the title to highlight the link between amino acid metabolism and cancer stem cells. Next, we generated a list (Table 2) of potential therapeutic targets involving amino acid metabolism to support the title; however, we do agree that the evidence or real perspectives into the associated therapeutic approaches are insufficient. According to your suggestion, we have tried our best to find and list some clinical trials in the revised manuscript that targeted amino acid metabolism in cancer stem cells to make its participation in cancer treatment plausible (Page 20, 21 yellow highlight). For example, sulfasalazine targets the cystine-glutamate antiporter xCT, parthenolide and piperlongumine target glutathione metabolism, and pegcrisantaspase depletes asparagine. All of these demonstrate the key role of amino acid metabolism in cancer stem cells and underscore their potential therapeutic prospects. We hope our response is convincing and can get your approval.

We are especially grateful to you for your helpful suggestions.

References:

1. Gao L, Xu W, Li T, Chen J, Shao A, Yan F, Chen G. Stem Cell Therapy: A Promising Therapeutic Method for Intracerebral Hemorrhage. *Cell Transplant* 2018; 27: 1809-1824 [PMID: 29871521 doi: 10.1177/0963689718773363].

2. Yamanaka S. Pluripotent Stem Cell-Based Cell Therapy-Promise and Challenges. *Cell Stem Cell* 2020; 27: 523-531 [PMID: 33007237 doi: 10.1016/j.stem.2020.09.014].

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: none

Response:

We really thank the reviewer for the positive comments about our manuscript. Thank you for your approval of this review!

Special thanks to you for your positive comments.

Responds to the editor's comments:

(1) Science editor:

I agreed with Reviewer #2 that this review should be rejected for publication on the World Journal of Stem Cells. The authors made an extensive review about amino acids metabolism and cancer stem cells. Although the manuscript is well written, it becomes very exhaustive and turns into a long list of amino acids and their correlation with some embryonic stem cells, cancer stem cells and tumor properties. No real perspective into novel therapeutic approaches is presented in the manuscript (thus the title does not really reflect the content of the manuscript), and other published articles have described similar data. There are inaccuracies about certain terms, such as the first sentence of the introduction which states: "Stem cells are pluripotent cells with...". However, most of stem cells are not pluripotent. Pluripotency characterizes embryonic (carcinoma) stem cells and iPSC, mostly. In my opinion, the manuscript does present enough originality to be published in its actual state.

Response:

Thank you very much for your comments and suggestions. They have helped us improve our manuscript significantly. Based on your suggestions, we have added more examples of clinical trials that targeted amino acid metabolism for cancer treatment. We hope that these supplements will more closely represent the title and the potential prospects of amino acid metabolism in cancer therapy. In addition, we have clarified the concept of stem cells after careful review. In order to better highlight the topic of cancer stem cells, we have removed the text that unintentionally conveyed incorrect concepts from the introduction section. We truly appreciate your suggestions.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Stem Cells, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report,

Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list.

Response:

Thank you very much for your affirmation of our manuscript. We have responded, peer-to-peer, to the comments from the editors and reviewers. Following your suggestion, we have compiled all the figures into a PowerPoint file along with the three-line tables. Additionally, since the figures are original, we have added "Copyright ©The Author(s) 2022" in the bottom right-hand side of the PowerPoint, as per your suggestion. We are extremely grateful to your recommendations. They have indeed made our manuscript more formalized and easier to read.

We have tried our best to improve the manuscript and make appropriate changes in it. We assure that these changes will not influence the content and framework of the paper.

We earnestly appreciate the Editors/Reviewers' extensive work and hope that our corrections will receive their approval.

Once again, thank you very much for your comments and suggestions.