

Dear Editor,

We are deeply grateful for your prompt reply to our manuscript entitled "Mesenchymal stem cells-derived exosomes for gastrointestinal cancer". We sincerely appreciate the constructive comments by you and professional reviewers. Based on your suggestions, the manuscript has been carefully revised, and hopefully our modified version would meet with your requirements and be published in World Journal of Gastrointestinal Oncology.

All the changes to the text have been marked in red in the revised manuscript. The responses to the comments are listed below in blue. In addition, the manuscript has been thoroughly checked before submission.

Thank you very much for your kind consideration. If you have any questions or comments, please feel free to contact us.

Sincerely yours,

Jiannan Li

Dear Reviewers,

Thank you so much for your valuable comments to our manuscript entitled "Mesenchymal stem cells-derived exosomes for gastrointestinal cancer". Your comments are very valuable and helpful for the improvement of our paper. According to your kind suggestions, we have revised the whole manuscript. We hope that this updated version will meet with your approval and be qualified to be published in World Journal of Gastrointestinal Oncology. All the changes to the text have been marked in red. The response to your comments is listed as follows.

Response to science editor:

1. Scientific quality: The manuscript describes a review of the mesenchymal stem cells-derived exosomes for the treatment of gastrointestinal cancer. The topic is within the scope of the WJSC.

Response: Thank you for your careful review. we have checked the manuscript throughout and revised manuscript based on your valuable comments.

1.1 Classification: Grade C and Grade C;

Response: Thanks for your notifications. We have revised the manuscript carefully based on your advice and hope that the revised manuscript will meet with approval.

1.2 Summary of the Peer-Review Report: The authors have summarized the effect of MSC exosomes on GI malignancies and their therapeutic potential. It is of interest. However, the questions raised by the reviewers should be answered.

Response: Thank you very much for your kind comments. We have provided a point-by-point response to reviewers' comments. We sincerely hope that this revised manuscript has addressed all your comments and suggestions.

1.3 Format: There is 1 table and 5 figures.

Response: Based on reviewers' comments, we have deleted 5 figures referenced from other sources and corresponding figure legends. We have revised the table carefully based on your advices.

1.4 References: A total of 122 references are cited, including 24 references published in the last 3 years;

Response: We have deleted 2 previous references and added 18 new references, and a total of 138 references are cited in the revised manuscript.

1.5 Self-cited references: There is 1 self-cited reference. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated

Response: Thanks for your notifications. The self-referencing rates of our revised manuscript meet the requirements of World Journal of Gastrointestinal Oncology.

1.6 References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.

Response: Thanks for your notifications. All peer reviewers did not request us to cite any improper references published by themselves, and we do believe all cited references are proper.

2. Language evaluation: Classification: Grade C and Grade A. A language editing certificate issued by AJE was provided.

Response: Thanks for your notifications. The English of this manuscript has been edited by a professional company and the current form is easier for readers to understand.

3. Academic norms and rules: No academic misconduct was found in the Bing search.

Response: Thank you for your careful review.

4. Supplementary comments: This is an unsolicited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJSC.

Response: Thank you for your careful review.

5.1 Supplementary comments: Issues raised: The language classification is Grade C. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>;

Response: We apologize for the language problems in the original manuscript. The English of this manuscript has been edited by a professional company.

5.2 The title is too long, and it should be no more than 18 words;

Response: Thanks for your notifications. We have we revised the title as "Mesenchymal stem cells-derived exosomes for gastrointestinal cancer".

5.3 The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

Response: Thanks for your notifications. We have uploaded the approved grant application forms, included the Science and Technology Development Project of Jilin

Province funding and the Youth Program of the National Natural Science Foundation of China funding. However, we are sorry for that the foundation did not provide any approval documents about the Education Project of Jilin University funding, so we cannot upload the approved grant application form about this funding.

5.4 The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Response: Thanks for your notifications. we have deleted all figures and figure legends based on reviewers' comments.

5.5 Please obtain permission for the use of picture(s). 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. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

Response: Thanks for your notifications. we have deleted 5 figures referenced from other sources and corresponding figure legends based on reviewers' comments.

6. Recommendation: Conditional acceptance.

Response: Thank you very much for your kind comments. We have revised the manuscript carefully based on reviewers' advice.

Response to Reviewer 1:

1. There is now an increase in in vivo and in vitro studies of exosomes derived from MSC, which may regulate tumorigenesis and metastasis. However, systematic reviews and books do not provide a full understanding. In this review manuscript, the effectiveness of MSC-derived exosomes for gastrointestinal cancers, and also digging into the features and functional mechanisms of exosomes. As the authors mentioned,

MSC-derived exosomes have opposite effects on tumors, which probably dependent on cancer cell types, tumor stages and body conditions as well as the origins of MSC. This manuscript appears these questionable controversial situation of MSC-derived exosomes, and increased focus and studies of the relationship between exosomes and cancers.

Response: Thank you very much for your kind comments.

Response to Reviewer 2:

1. The authors have summarized the effect of MSC exosomes on GI malignancies and their therapeutic potential. the manuscript is of interest to the scientific community, however, it cannot be accepted without some improvements.

Response: Thank you very much for your suggestion. We have revised the manuscript carefully based on your advice.

2. In the abstract, the authors claim that MSCs play role in regulating GI cancer through paracrine only which is not the case!!!!

Response: Thank you very much for your suggestion. We all agree with your advice that MSCs play role in regulating GI cancer through paracrine only which is not the case, which also includes autocrine mechanisms, direct contacts with tumor cells, as well as other still unclear ways. We thank you to raise this important issue. We have revised the Abstract and substituted the term “through paracrine” to “through multiple mechanisms, such as secreting cytokines and direct interactions.”

3. The manuscript needs extensive English editing some of which are and not limited to below:

Response: We thank you to raise this important issue. The English of this manuscript has been edited by a professional company and we also revised all the manuscript carefully based on your advice.

3.1 Last paragraph of the abstract. have shown extremely potential, delete extremely; the same applies to the first sentence of the core tip.

Response: Thanks for your advice, we have deleted the word “extremely” in these two sentences.

3.2 There is lot of repetition; In the intro: on the one hand repeated on two consecutive sentences.

Response: Thanks for your advice, we have deleted the phrases “on the one hand” and rewritten these two sentences as follow.

“A series of literature has been reported that MSCs are capable of promoting tumor progression through secreting pro-tumorigenic factors^[15] and differentiating into cancer-associated fibroblasts^[16, 17]. Nevertheless, other evidence suggests that MSCs could suppress tumor proliferation via secreting cycle inhibitor P21 and anti-tumorigenic factors such as interleukins, IFN- γ , Dkk-1, and promote tumor cell apoptosis through secreting apoptotic executor caspase 3 (CASP3)^[18, 19].”

3.3 In section 3: For example and for instance has been repeated more than 3 times.

Response: Thanks for your advice, we have revised this section carefully.

3.4 Line 135 is not clear, should rewritten.

Response: Thank you very much for your advice. We have rewritten this sentence as follow.

“Interestingly, exosomes can play a dual role in tumorigenesis, both anti-tumor and pro-tumor, which may be due to that the exosomes can be derived from different tissues^[41].”

3.5 Line 94: in vitro experimenets instead of cell experiments.

Response: We have substituted the term “cell experiments” to “in vitro experiments” in this sentence.

3.6 Line 163: the next section not chapter

Response: We have substituted the term “chapter” to “section” in this sentence.

3.7 Line 170: increasing not increases.

Response: We have substituted the term “increases” to “increasing” in this sentence.

3.8 Line 173: has been rewritten, check attached file delete line 176 (no need for it)

Response: We thank you to raise this important issue. In this section, we aimed to emphasize the importance of chemotherapy for GC treatment, then to address the major treatment obstacles: chemoresistance. However, we are really sorry for the inaccurate description. As a result, we have deleted Line 173 and Line 176, then we revised this section carefully as follow.

“In the current treatments of GC, the perioperative or adjuvant chemotherapy can significantly improve the therapeutic effect on advanced GC^[53]. However, chemoresistance is one of the major obstacles^[54].”

3.9 Line 509: spelling mistake, line 510: showing.

Response: We have corrected the spelling mistake in Line 509 and substituted the term “shown” to “showing” in Line 510.

4. I have serious concern about using other people's work such as in the figures without permission and without any alterations. I am against using those figures in your review.

Response: Thanks for your advice, we all agree with your advice. we have deleted all figures and figure legends.

5. Add to the table a column named references to add the used references.

Response: We are really sorry. The column named references has already been provided. The reason why you cannot find it is that the last column is out of the visual area. We have resized the table.

6. For epidemiological data, use the latest updates.

Response: Thanks for your advice. Following your advice, we have revised all epidemiological data based on the latest updates.

7. Lot of missing references especially in the discussion.

Response: We are really sorry for this. We have added references for all manuscript carefully, especially in the Discussion section.