

Dear Editor,

We are deeply grateful for your prompt reply to our manuscript entitled "The efficacy of mesenchymal stem cells in the treatment of gastrointestinal malignancies". 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.

We have revised Figure 4 in our manuscript. All the five figures are re-using figures published elsewhere. However, all the figures are derived from open access journal articles in which the figures can be used freely. As a result, we haven't provided documentation that the previous publisher or copyright holder has given permission for the figure to be re-published. If this is still appropriate, it is really nice to help us to delete all the figures.

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,

Kai Zhang

Dear Reviewers,

Thank you so much for your valuable comments to our manuscript entitled "The efficacy of mesenchymal stem cells in the treatment of gastrointestinal malignancies". 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 Reviewer 1:

1. Well written paper on an interesting subject.

Response: Thank you very much for your kind comments.

Response to Reviewer 2:

1. This is an interesting study about the efficacy of mesenchymal stem cells in the treatment of gastrointestinal malignancies.

Response: Thank you very much for your kind comments.

Response to Reviewer 3:

1. In this manuscript the authors carry out a systematic review on the efficacy of mesenchymal stem cells (MSCs) in the treatment of gastrointestinal malignancies. The topic is interesting but there are some criticisms.

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

2. In the text when a sentence begins with the author's name followed by et al, it is mandatory to put the name of the first author, then et al and then the reference in brackets. Instead the authors of the manuscript put the name of the last author (and not the first) followed by et al and the reference is often placed at the end of the sentence. For example, the authors state "Zhang et al. found that hMSCs depressed H7402 proliferation by downregulating the mRNA level of NF- κ B [71]." Reference [71] is L. Qiao, T.-j. Zhao, F.-z. Wang, C.-l. Shan, L.-h. Ye, X.-d. Zhang, NF-kappa B

downregulation may be involved the depression of tumor cell proliferation mediated by human mesenchymal stem cells, *Acta Pharmacologica Sinica* 29(3) (2008) 333-340.” Zhang is the last name and not the first name and reference is at the end of sentence. The corretct sentence is “Qiao et al. [71] found that hMSCs depressed H7402 proliferation by downregulating the mRNA level of NF- κ B.”. Please correct throughout the manuscript.

Response: Thank you very much for your advice. We have made all the corrections throughout the manuscript.

3. In Table 1 please replace PC with pancreatic cancer and CRC with colorectal cancer.

Response: Thank you very much for your suggestions. We have replaced PC with pancreatic cancer and CRC with colorectal cancer.

4. In Table 1 it would be necessary to highlight in the title that are listed only in vitro studies.

Response: Thanks for your advice. However, some researches listed in Table 1 included animal studies which was performed *in vivo*. As a result, we revised the title as “The effect of mesenchymal stem cells in the treatment of gastrointestinal malignancies in vitro and in vivo.”

5. In paragraph “MSCs” the authors state “and cord blood stem cells, which include 2 subtypes, namely, hematopoietic stem cells and MSCs”. Hematopoietic stem cells and MSCs derived not only from cord blood stem cells but also and mostly from bone marrow. Please correct this sentence.

Response: In this sentence, we aimed to present that stem cells can divide into cord blood stem cells, which include hematopoietic stem cells and MSCs. Indeed, hematopoietic stem cells and MSCs derived not only from cord blood stem cells but also and mostly from bone marrow. We have revised this sentence as follow.

“and cord blood stem cells, including hematopoietic stem cells and MSCs which are mostly derived from bone marrow”.

6. In paragraph “MSCs” the authors state “In a specific microenvironment, MSCs can differentiate into mesodermal-derived cells, such as osteoblasts, chondrocytes,

adipocytes, tendon cells, and muscle cells [27]. This sentence is a repetition. Please delete.

Response: Thanks for your advice, we have deleted this sentence.

7. The neural differentiation of MSC is still under discussion today. It is not enough to express neuronal markers but it is necessary to have electrophysiology experiments. For this reason, MSC neural differentiation it cannot be simply described with the sentence “In Liu’s study, MSCs differentiated into neural stem cells and immature neurons, which specifically expressed Nestin and β -Tubulin III, respectively [30]. Doubts about the real differentiation should be highlighted by the authors.

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

“Liu *et al.*^[30] found that MSCs could differentiate into neural stem cells and immature neurons.”

8. In paragraph “MSCs for gastric cancer” the authors state “BMSCs, which are a type of stem cell found in bone marrow, possess differentiation features and migration tendencies towards tumour tissues. BMSCs can release various kinds of cytokines to affect tumour growth...”. Please modify the sentence because this concept has been repeated several times.

Response: We are really sorry that the sentence has been repeated several times. As a result, we have deleted this sentence.

9. Throughout the manuscript the authors often do not indicate the species from which the stem cells derive. Please specify.

Response: Following your advice, we have added the species from which the stem cells were derived in all the manuscript.

10. The authors use the term “scholar”. Please substitute this term.

Response: We have substituted the term “scholar” to “researchers” in all the manuscript.

11. In paragraph “MSCs for hepatoma” the author state “Other studies have also shown that MSCs prevent hepatoma growth via the Wnt signalling pathway.” Please add references.

Response: Thanks for your advice. We have added references for this sentence.

12. In “Discussion” the conclusions of the authors are rather obvious and add nothing to what is already known in the literature. In this manuscript the authors list articles and report their results, but a discussion of the data of the different articles is completely missing. This makes reading difficult.

Response: We are really sorry for this. Based on your advice, we have added some discussion of the data of different articles in the whole manuscript which can support our “Discussion” part.

13. The manuscript should be rewritten considering what has been said previously. Please not only a list.

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