

Dear Editors and Reviewers,

I am glad to receive your letter. Thank you very much for your hard work and kind suggestions. I have read the comments carefully and revised the manuscript according to your suggestions. Thanks again for your excellent work.

The main corrections in the paper and the responds to the reviewer's comments are as following:

Editor Comments to Author (if any):

Thanks for your valuable comments and suggestions which have led to significant improvement on the presentation and quality of this paper. The following are point-by-point responses to your concerns. And we shall detail the changes we have made on the paper.

Science editor's comment to author:

Response to Science editor:

1 Scientific quality: The manuscript describes a review of the effect of metformin on stem cells: Molecular mechanism and clinical prospect. The topic is within the scope of the WJSC. (1) Classification: Grade C; (2) Summary of the Peer-Review Report: The paper is reasonable, reviewer suggest listing all the conditions on the role of metformin/SC in osteogenic differentiation, neuronal differentiation, myogenic and muscle regeneration, aging, cancer stem cell etc. in a summary table listing all discussed conditions, cell type or model, relevant reference number and suggested mechanisms. It would be useful to add more the role of metformin and stem cells in tissue injury healing, e.g. gastric ulcer and ulcerative colitis in which stem cells play

significant role; and (3) Format: There are 0 tables and 0 figures. A total of 119 references are cited, including 46 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade B. A language editing certificate issued by Edanz's was provided. 3 Academic norms and rules: The authors provided the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an invited manuscript. The study was supported by the National Natural Science Foundation of China. The topic has not previously been published in the WJSC. The corresponding author has 1 published articles in the BPG. 5 Issues raised: I found 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) 6 Re-Review: Required. 7 Recommendation: Conditionally accepted._

Reply : Thanks for your advice. The manuscript has been revised following your suggestion.

Editorial office director's comment to author:

Response to Editorial office director:

I have checked the comments written by the science editor. The authors need to add some figures or tables.

Reply: Thanks for your advice. We have added the one figure and one table following your suggestion.

Company editor-in-chief's comment to author:

Response to Company editor-in-chief::

I have reviewed the Peer-Review Report, the full text of the manuscript

and the relevant ethics documents, all of which have met the basic publishing requirements, and the manuscript is conditionally accepted with major revisions. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report and the Criteria for Manuscript Revision by Authors. Before final acceptance, authors need to correct the issues raised by the editor to meet the publishing requirements. Re-Review: Required.

Reply : Thanks for your advice. The manuscript has been revised following your suggestion.

Reviewer(s)' Comments to Author:

Response to Reviewer #1:

Thanks for your valuable comments and suggestions which have led to significant improvement on the presentation and quality of this paper. The following are point-by-point responses to your concerns. And we shall detail the changes we have made on the paper.

1. Listing all the conditions on the role of metformin/SC in osteogenic differentiation, neuronal differentiation, myogenic and muscle regeneration, aging, cancer stem cell etc. in a summary table listing all discussed conditions, cell type or model, relevant reference number and suggested mechanisms.

Reply: Many thanks for your kind comments. We have added the table following your suggestion.

2. It would be useful to add more the role of metformin and stem cells in tissue injury healing, e.g. gastric ulcer and ulcerative colitis in which stem cells play significant role. Possibly, the mechanisms are different from the effect on cancer stem cells.

Reply: Thanks for your kind comments. The opinion is extremely important to us. We have discussed the role of metformin and stem cells in tissue injury healing in the revised manuscript following your suggestion. Please see page 12 of the revised manuscript.

3. Add a diagram showing stem cells and the mechanisms of their activation, differentiation and migration/chemoattraction (e.g. SDF-1, CXCR4) and the role of metformin in these processes, e.g., direct effect of metformin on the mitochondria to inhibit oxidative phosphorylation and reduce mitochondrial ATP production. Stromal cell-derived factor-1 (SDF-1) and its receptor CXCR4 have been demonstrated to play an important role in the "homing" of BMD-EPC to injured sites and neovascularization in tissue repair.

Reply: Thanks for your valuable comments. We have added the diagram following your suggestion.

4. Metformin may affect many of these conditions by acting also through other mechanisms not related to stem cells' actions.

Reply: Thanks for your comments. We have discussed the effect of metformin on somatic cells in the revised manuscript following your suggestion. Please see page 21 and 22 of the revised manuscript.

5. These suggested revisions would significantly improve the paper quality, its readability and would be appreciated by the readers. The authors may also use some of below references: Yongchen Liu Zheng Wang Maolan Li Yuanyuan Ye Yi Xu Yichi Zhang Ruiyan Yuan Yunpeng Jin Yajuan Hao Lin Jiang Yunping Hu Shili Chen Fatao Liu Yijian Zhang Wenguang Wu Yingbin Liu. Chloride intracellular channel 1 regulates the antineoplastic effects of

metformin in gallbladder cancer cells. Cancer Science. April 2017
<https://doi.org/10.1111/cas.13248> Shawky LM, El Bana EA, Morsi AA. Stem
cells and metformin synergistically promote healing in experimentally
induced cutaneous wound injury in diabetic rats. Folia Histochem Cytobiol.
2019;57(3):127-138. doi: 10.5603/FHC.a2019.0014. Epub 2019 Sep 6. PMID:
31489604 Courtois S, Durán RV, Giraud J, Sifré E, Izotte J, Mégraud F,
Lehours P, Varon C, Bessède E. Metformin targets gastric cancer stem cells.
Eur J Cancer. 2017 Oct;84:193-201. doi: 10.1016/j.ejca.2017.07.020. Epub 2017
Aug 17. PMID: 28822889

Reply: Thanks for your advice. The suggested references are extremely valuable to the manuscript. These recommended references are cited in the revised manuscript. Please see page 12, 15 and 22.

52 Shawky LM, El BE, Morsi AA. Stem cells and metformin synergistically promote healing in experimentally induced cutaneous wound injury in diabetic rats. *Folia Histochem Cytobiol* 2019; 57: 127-138 [PMID: 31489604 DOI: 10.5603/FHC.a2019.0014]

76 Courtois S, Duran RV, Giraud J, Sifre E, Izotte J, Megraud F, Lehours P, Varon C, Bessede E. Metformin targets gastric cancer stem cells. *Eur J Cancer* 2017; 84: 193-201 [PMID: 28822889 DOI: 10.1016/j.ejca.2017.07.020]

122 Liu Y, Wang Z, Li M, Ye Y, Xu Y, Zhang Y, Yuan R, Jin Y, Hao Y, Jiang L, Hu Y, Chen S, Liu F, Zhang Y, Wu W, Liu Y. Chloride intracellular channel 1 regulates the antineoplastic effects of metformin in gallbladder cancer cells. *Cancer Sci* 2017; 108: 1240-1252 [PMID: 28378944 PMCID: PMC5480064 DOI: 10.1111/cas.13248]

If you have any question, please don't hesitate to contact me.

With best regards,

Yours Sincerely

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