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PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 77808

Title: Intercellular mitochondrial transfer as a means of revitalizing injured glomerular endothelial cells

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05489967
Position: Peer Reviewer
Academic degree: PhD
Professional title: Research Scientist
Reviewer's Country/Territory: United States
Author's Country/Territory: China

Manuscript submission date: 2022-05-23

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-05-31 02:31

Reviewer performed review: 2022-06-06 22:00

Review time: 6 Days and 19 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Dear authors, The authors are reporting the treatment of diabetic kidney diseases (DKD) with bone marrow stem cells. In vitro, co-culture of BMSC with injured glomerular endothelial cells decreased the level of injury, rescue the mitochondria activity, increase the cell proliferation. The rescue is shown to be due to the BMSC mitochondrial transfer, in a 1 to 1 ratio in vitro study. In a DKD rat model, BMSC were injected, and the level of kidney injury was reported, 2 weeks after the injection. The manuscript is well written and easy to read. However, I have comments for the authors. - Do the authors know what is the percentage of GEG cells that were transferred with BMSC mitochondria? Did the authors noticed a stronger effect on the transferred cells (fig 1B and C) compared to non-transferred cells? - Figure 1: The ration Bcl-2 /Bax should be included, because more informative about anti-apoptotic effect of BMSC on GEG cells. - The authors refered to an old publication to explain the protocol to isolate the BMSC (reference 19). However, the authors must provide the source of BMSC. Are they rats? If so, is the treatment autologous or allogeneic? If the BMSC are humans, what is the IRB approved human protocol? - One of the major concerns is the title. The authors claims that mitochondria transfer from MSC rescues the injured glomerular endothelial cells in vitro but also in vivo. However, the authors have no proof that the in vivo rescue is due to mitochondria transfer. Many other factors (paracrine, transfer of extracellular vesicles, exosomes, MSC differentiation) could be factors that rescue the kidney. The authors should modify the title, the discussion, and the conclusion, based on my comments. - It is well known the biodistribution of BMSC can be all over the body, after injection, especially in the lungs. Did the authors study the biodistribution of the BMSC, after

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injection and how many BMSC were alive in a time course manner after the injection? - This question is related to the previous one. In figure 4, the authors claimed TUNEL and histopathology analysis of tissues from all rats, but only the kidney was studied. Histopathology of other organs, such as heart and lungs, should be added to show the safety of the BMSC injection. - Did the author measured the level of liver injury by studying the level of AST and ALT in the blood, that could be associated with diabetic kidney diseases? - It is not clear if the injected BMSC were dyed or not. Can the authors specify it in the Materials and Methods section?

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Position: Peer Reviewer
Academic degree: DDS, Doctor, MD
Professional title: Doctor
Reviewer's Country/Territory: Indonesia
Author's Country/Territory: China

Manuscript submission date: 2022-05-23

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-06-17 15:12

Reviewer performed review: 2022-06-17 18:55

Review time: 3 Hours

Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

I would like to congratulate the authors for this manuscript. It is interesting and can bring new perspective. I have some comments: In the materials and methods on page 7, BMSCs passage 2-4 were used, while in the last sentence passage 2-3 were used. Which ones were used in the experiment? Please clarify and give reasoning for using multiple passage cells. Please add the location and country of the materials accordingly, some of them were not completely provided. Page 17 line 9 "...figure 4E and 5F..." should be "...figure 4E and 4F...". Please revise accordingly. References number 40-43 are not available in the text, they can be added in the methodology.