RE: NO: 87048

TITLE: Potential of dental pulp stem cells and their products in promoting peripheral nerve regeneration and future applications

Dear Editorial Office and reviewer(s),

Thanks a lot for your great efforts. We have revised the manuscript according to the peer review report and editorial comments. On the next pages, our point-to-point responses to the issues raised by the reviewers are listed.

EDITORIAL OFFICE'S COMMENTS

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

Reply: Thank you for your great efforts and comments. The following is a point-by-point response to each question raised in the peer review report, and the revised/added content is highlighted with yellow in the revised manuscript.

2. The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company.

Reply: This article has been edited by one professional language editing company (American Journal Experts, AJE), which is recommended by your journal, and the solution we chose is advanced editing. I will upload the new Editing Certificate.

3. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript.

Reply: We supplemented and improved the highlights of the latest cutting-edge research results by applying reference citation analysis (RCA) and further improved the content of the manuscript according to peer review (Ref: [48], [50], [55], [57], [59], [60], [61], [91], [106], [112], [121], [125], [136]).

4. Uniform presentation should be used for figures showing the same or similar contents; for example, “Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...”.

Reply: Thank you for your comment. I have revised the figures. Please kindly refer to Figure 2, Figure 3 and Figure 4.

5. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. 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) 2023.

Reply: We have uploaded the main figures in a decomposable form (all components are movable and editable) and organized them into a single PowerPoint file (with relevant copyright information). However, our figures were originally created with BioRender.com. This website can export high-quality PDF, PNG and JPG file formats, but its compatibility with PowerPoint is limited. If there is anything that needs to be modified, we can modify the figures at any time, or we can share the figures online through BioRender.com. I have uploaded the relevant copyright license certificate to the supplementary document and provided complete high-definition figures in PPT.

I’m very excited that I could have a precious opportunity to revise my manuscript. Contact me anytime if needed, the Authors are open for further improvements if anything is still not publish-ready.

Peer-Reviewer comments:

Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors:
1. The manuscript entitled “Application of dental pulp stem cells in peripheral nerve injury" appears to be interesting. The research presented in the current manuscript would be on interest to many scientific groups with similar scientific interests, therefore, I recommend publishing this paper, but after revisions.

Reply: Thank you for your comments and recognition. We have revised the article according to your comments and suggestions.

2. Title: the title is not appropriate. I suggest making up it.

Reply: We have changed the title to "Potential of dental pulp stem cells and their products in promoting peripheral nerve regeneration and future applications".

3. Abstract: The abstract is presented well with logically defined concept of the work.

Reply: Thank you for your approval.

4. Introduction: Introduction part describes topic-related information and clearly discloses the object of the work. I think some parts (i.e., "Differentiation into endothelial cells") is short.

Reply: Thank you for your comments. We expanded this part (differentiation into endothelial cells) and highlighted it in yellow in the revised manuscript. At the same time, other parts are supplemented according to the latest literature.

5. Instead, the authors should elaborate more regarding new papers.

Reply: Thank you for your advice. We supplement and improve the highlights of the latest cutting-edge research results by applying reference citation analysis (RCA) (Ref: [48], [50], [55], [57], [59], [60], [61], [91], [106], [112], [121], [125], [136]).

6. The main theme of the manuscript should be represented with the help of several figures.

Reply: Thank you for your advice. We added Figure 1 to show the advantages of DPSCs as alternative stem cells for nerve regeneration. In addition, figure 2 is used to explain the differentiation ability of DPSCs. Figure 3 is used to explain the role of DPSCs and their products in peripheral nerve injury. Figure 4 is used to illustrate the main models of the current research on DPSCs.

7. Conclusion: Please add more comments on this section and indicate the possibilities of the practical use of the results.

Reply: Thank you for your advice. We expanded the conclusion section and highlighted it in yellow in the revised manuscript. We focus on the nerve regeneration ability of DPSCs, the advantages of practical use, current

difficulties and future prospects. We obtained the following results: DOSCs can bring good news to PNI patients.

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade C (A great deal of language polishing)
Conclusion: Minor revision
Specific Comments to Authors: Dr. Xing et al. have submitted a narrative review entitled "Application of dental pulp stem cells (DPSCs) in peripheral nerve injury" for publication in WJSC. Based on the published data, the authors conclude that DPSCs can be a superior choice for treating peripheral nerve injury. Besides, the authors also claim that DPSCs-derived paracrine secretions can be used for cell-free therapy of peripheral nerve injury. I have the following comments.
1. • Firstly, the title of the narrative review can be improved to read more novel.

Reply: Thank you for your advice. We changed the title of this review to "Potential of dental pulp stem cells and their products in promoting peripheral nerve regeneration and future applications".

2. • The authors have attempted to justify the superior properties of DPSCs for cell-based therapy. However, there is little comparison between MSCs derived from other tissue sources in general and bone marrow (BM)- and umbilical cord (UC)-)-derived MSCs that have already reached the clinical setting. Authors must include a paragraph comparing MSCs from BM and UC to justify that DPSCs are superior.

Reply: Thank you for your advice. We added a paragraph in the article to illustrate the advantages of DPSCs. By comparing BM and UC, DPSCs have a higher value-added rate, easier access and stronger differentiation ability. DPSCs are a good substitute for stem cells to treat peripheral nerve injury. The specific added content is in the fifth paragraph under the heading of "Stem cell therapy for PNI", and the added content is highlighted with yellow in the revised manuscript.

3. • The Tables need to be significantly improved in presentation. The studies included in the Tables are haphazardly organized for animal and human studies. For example, in Table 1, the first three studies are human cells followed by a rat study, and then human again. Similarly, the results/ outcome in the Tables can be more elaborate.

Reply: Thank you for your advice. We reordered the tables based on "Cell donor" and "Year published" and made the results section more detailed. The

revised content is highlighted in yellow in the revised manuscript.

4. • BM-MSCs are known to have rich paracrine activity, and so do DPSCs. How is their secretome similar or better in terms of bioactive molecules? How do their insoluble paracrine components (exosomes) differ in their payload?

Reply: Thank you for your question. Both DPSCs and BM-MSCs can secrete abundant neurotrophic factors, such as BDNF and GDNF. DPSCs showed higher levels of neurotrophic factors and angiogenic factors in the same environment, and their nutritional role in angiogenesis, neurite extension, migration and anti-apoptosis was higher than that of BM-MSCs in the same environment. Exosomes derived from DPSCs can inhibit the differentiation of CD4+ T cells into helper T cells 17, reduce the secretion of the proinflammatory factors IL-17 and TNF-α, promote the polarization of CD4+ T cells into Tregs, and increase the release of the anti-inflammatory factors IL-10 and TGF-β. Compared with BM-derived exosomes, DPSCs have a stronger immunoregulatory ability. Exosomes from DPSCs/BM-MSCs significantly reduced the activity of caspase3/7 and showed a significant antiapoptotic effect. The composition of exosomes is complex, and the specific effective components to promote nerve regeneration still need much research. The composition of secretions will be different in different environments. At present, many studies show that the neuroprotective ability of DPSC exosomes is better than that of bone marrow mesenchymal stem cells. I added this part to the fourth paragraph under the heading "Cell-free therapeutic alternatives involving DPSCs", and the added content is highlighted with yellow in the revised manuscript.

5. • It would be interesting if the authors included studies that directly compare the reparability of DPSCs with MSCs from other tissue sources.

Reply: Thank you for your advice. We increased the comparison of DPSCs with other stem cells. These include dental follicles and papilla-derived stem cells, BM-MSCs, adipose tissue-derived stem cells, synovial fluid-derived stem cells, and umbilical cord stem cells. The addition is located in the sixth natural paragraph under the heading "Stem cell therapy for PNI". The neural regeneration ability of adipose tissue-derived stem cells, muscle-derived stem cells and other dental stem cells is also introduced under this heading. The added content is highlighted with yellow in the revised manuscript.

6. • The Figure quality may be improved.

Reply: Thank you for your advice. Based on the peer review, we added Figure 1 to illustrate the advantages of DPSCs. Uniform presentation has been used

for figures showing the same or similar contents, and we have improved the resolution of the picture. If other changes are needed, we will actively revise them.

7. • The manuscript needs to be extensively revised for grammar and syntax to make it have a better flow for the reader.

Reply: Thank you for your comments. We have revised the grammar and syntax of the manuscript. To meet the requirements of periodicals and give readers a better reading experience. This article has been edited by one professional language editing company that is recommended by the journal, and the solution we chose is advanced editing. The manuscript was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors.

Your sincerely,
Wen-Bo Xing