

Dear editor and reviewers,

Please accept our sincere gratitude for reviewing “**Priming Strategies for Controlling Stem Cell Fate: Applications and Challenges in Dental Tissue Regeneration**” (Manuscript NO: 65029). We have modified the manuscript in response to your comments. Revisions are marked in red in the revised version. Additionally, our responses to your comments are included below.

We thank you again for these reviews, which have certainly helped to further improve our manuscript. We hope that you find our revisions satisfactory, and we look forward to the acceptance of our manuscript.

Dr. Yang

May 14, 2021

Responses to Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The present manuscript entitled " Priming Strategies for Controlling Stem Cell Fate: Applications and Challenges in Dental Tissue Regeneration" was examined. The author reviewed many studies that were published in the regulation of MSCs that are summarized in the manuscript. After careful evaluation, some suggestions are listed below and this manuscript still needs to upgrade.

Response:

Thank you for the general comments. Based on the comments of all reviewers we have intensively revised the manuscript. We have added additional information and tried to sharpen the line of argumentation. We hope that this has improved the manuscript substantially.

Main comment 1:

The manuscript rarely refer to the tissue regeneration, thus, it doesn't correspond to the question very well.

Response:

In this review, we aim to summarize the current priming approaches to regulate stem cell fate for cell-based tissue regeneration. In our concept, application of regenerative medicine should not be performed without comprehensive understanding of biological events required for the process of regeneration. Tissue regeneration is a complex and dynamic biological process and consists of a sequence of cellular and molecular events. The initial step of the process involves the activation of stem cells. In this context, understanding how the biological, biophysical, and biochemical cues to regulate stem cell behavior involved in the process of new tissue formation is essential. The knowledge of the MSC behavior is the key for the application of tissue engineering. At present, there are many scientific advances in the field of primed MSCs. Therefore, this is a short review of the current state of this topic, with the purpose of showing insights of dental tissue regeneration.

Main comment 2:

Towards the regulation of MSCs, chemical and physical factors also play very vital roles besides biological agents. Therefore, I think it is better to supplement the related research work.

Response:

Thanks for your suggestion. We supplement the part of "mechanical and physical stimuli" in our manuscript ([Page 12-13](#)). For the chemical factors, we have already included the frequently used chemicals or pharmacological agents that induce hypoxia condition in the part of "hypoxia preconditioning" ([Page 9](#)). The other chemicals are seldom investigated in the field of dental

regeneration. Therefore, we do not organize “chemical factors” as the independent part in our manuscript.

Main comment 3:

This review lack of the personal perspective of the authors.

Response:

We have revised the ‘CONCLUSION’ section and discussed more about our perspectives.

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Main comment 4:

There are some grammar mistakes, for example, the tense problems, and it is necessary to improve the written English.

Response:

We revised the manuscript by academic language editing service and provided the language certification.

Responses to Reviewer #2:**General comment:**

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Manuscript ID65029 reviews different priming approaches to increase MSC regenerative and immunomodulatory activities. In general, this manuscript is very well organized and comprehensive. It covers most of the essential aspect of MSC biology. The text is fluid, however, it lacks some more descriptive figures on priming subjects. Although this manuscript is very interesting, the following points need to be clarified.

Response:

We thank the reviewer for the feedback. The other comments have been addressed below.

Main comment 1:

In the introduction, the authors have mentioned the MSC capacity of differentiation. However, recent studies demonstrate their potential to differentiate into an even larger range of cell types such as endothelial cells and especially hepatocytes which makes them even more interesting in the field of regenerative medicine. The following article could help you to build up this section. (PMID: 32033595 and PMID: 29763649)

Response:

Revisions are made according to the reviewer's comment. We described the MSC capability of differentiation into more specialized cells such as endothelial cells, hepatocytes, neurons, and myoblasts. Moreover, we reorganized the section of MSC capabilities to make it clearer and more understandable.

[Page 4. Line 40-48](#)

Main comment 2:

In Figure 1, for demonstrating the immunoregulatory function of MSCs, the authors have depicted only macrophages. MSC ability to control T cells have been discussed more extensively than other cells.

Response:

We redraw Figure 1 and depicted more details concerning MSC immunomodulation. We also revised its figure legends.

Main comment 3:

Concerning TNFa priming: very recent publications demonstrate the strong involvement of the TNF-TNFR2 singling pathway and not TNF-TNFR1 in MSC regenerative and immunomodulatory effects. This includes their pro-angiogenic function, the suppression of T cells, induction of Tregs, and changing their T cell cytokine production pattern. Moreover, TNFR2 expression were corelated with NF-kB which is also mentioned by the authors to be essential after TNF pre-treatment. The following articles cover this important aspect since the main focus of this review is on priming effects. (PMID: 33344453, PMID: 32669116, PMID: 33303019)

Response:

Thank you very much for the suggestions! We have revised the manuscript, supplemented the references, and discussed them in detail. We have also added some discussions regarding the MSC immunomodulation of T cells. We hope that MSC immunomodulatory functions could be clearly present in this way.

[Page 13-15](#)

Main comments 4:

One of the crucial mechanisms of action of MSC immunoregulatory function is via induction of Treg. The authors did not discuss this point. Moreover the coverage on T cell suppression is very poor and needs more attention.

Response:

We have intensively revised the cytokines priming section to discuss the T cell suppression. Please see changes within the revised manuscript.

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Responses to Reviewer #3:**General comment:**

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

In this review article, the authors summarize the priming approaches of dental tissue-derived MSCs to improve the therapeutic effects of MSCs in dental tissue regeneration. The priming approaches include priming culture conditions, preconditioning by cytokines and growth factors, and genetic modification of MSCs. They summarized well not only the tremendous progress, but also challenges of the current approaches in the field. This article is acceptable for publication in World Journal of Stem Cells.

Response:

We appreciate the highly positive feedback from the reviewer for our manuscript. Thanks a lot!

Minor comment:

There is no major comments, but some minor corrections need to be made in terms of English expressions, for example ‘dental-derived MSC’ should be ‘dental tissue-derived MSC’ in the second paragraph on page 5 and ‘a sufficient number’ should be ‘a sufficient number of cells’ in the last paragraph on page 7.

Response:

We are sorry for the confusion. Revisions concerning language issues are made according to the reviewer’s comment. We replaced ‘dental-derived MSC’ by ‘dental tissue-derived MSC’ and ‘a sufficient number’ by ‘a sufficient number of cells’.