

Replies to Reviewers

We would like to thank the reviewers for the constructive and positive comments, and we will respond point by point to the comments as listed below.

Reviewer: 1

Comments to the Author

This is an interesting and well written review manuscript focused on the possible clinical application of stem cells of different origin in the management of both oral and neurological diseases. The work is interesting, well written and well organized. The topic is very important, and I believe it matches well with the journal aims and scope of World Journal of Stem Cells. Please see below several comments for improving the manuscript.

Major comments

1. I suggest introducing more recent and up to date references, including reviews, in the field of stem cells and regenerative medicine. I can suggest PMID: 36034728, PMID: 35813047, PMID: 36238449, PMID: 35721599, PMID: 35607403

Response: Thanks for your good advice. We have added more related references in our manuscript. Please see underlined sentences in *INTRODUCTION* part (page 4, 6); *CONCLUSION* part (page 17).

2. oral and neurological diseases are I general quite distant research topics. I suggest the authors make an effort in formulating a more detailed rational behind the selection of these two research topics, both in the abstract and at the end of the introduction (as review aim). The common denominator is well explained in throughout the review and in the conclusion section, but, for a better reading and review understanding, it should be emphasized in the abstract and introduction.

Response: Thanks for your kind advice. We have emphasized the reasons for choosing these two research topics in the abstract and at the end of the introduction. We also drew the Figure 2 to show the relationship and mechanism. DFSCs are dental tissue-derived stem cells with advantages for the treatment of oral diseases; Moreover, DFSCs originating from the craniofacial neural crest exhibit neuro-ectodermal features, suggesting that an advantages for the treatment of neurological diseases. Please see underlined sentences in *Abstract* part (page 3); underlined sentences in *INTRODUCTION* part (page 7).

3. Besides the already mentioned the oral diseases, I suggest including cancers of the oral cavity, authors can check PMID: 35846142

Response: Thanks for your kind advice. This review mainly focuses on the pro-regeneration and anti-inflammation effects of DFSCs in

periodontitis, pulp necrosis, neurotrauma and neurodegenerative disease. For the treatment of cancer, as mentioned in this reference (PMID:35846142), MSCs can specifically migrate to tumor sites. However, MSCs that migrate to tumor sites have been reported to promote or inhibit tumor growth. As a result, it is difficult to apply unmodified mesenchymal stem cells to treat cancer. Consequently, there are broad prospects for using genetically engineered MSCs or MSCs as cell carriers for cancer treatment. To date, there have been no reports of DFSCs being used to treat cancer. By reasons of the foregoing, we did not discuss the application of DFSCs to cancer treatment in this manuscript.

Minor observations

1. Citations should be separated from the last word of the sentence. Please check the entire manuscript.

Response: Thanks for your kind advice. We have checked the article published in the World Journal of Stem Cells and there is no space between the citation and the last word of the sentence.

2. In the introduction, a supporting reference should be included for every stem cell type being mentioned

Response: Thanks for your good advice. We have added the supporting reference for each stem cell type. Please see references [17-35] in

INTRODUCTION part on page 6.

3. *Introduction, this important reference on the molecular mechanisms of osteogenic differentiation of mesenchymal stem cells should be included*
PMID: 33898434

Response: Thanks for your kind advice. We have added related content to *CONCLUSION* part. Please see underlined sentences in *CONCLUSION* part (page 18).

4. *The sub-head titles ORAL DISEASES and NEUROLOGICAL DISEASES should be improved with some terms referring to the use of stem cells for managing these diseases (as detailed in the paragraphs), otherwise in the current form it seems an introductive description of oral/neurological diseases*

Response: Thanks for your kind advice. We have modified the subtitles. Please see the subtitles as *ORAL DISEASES AND FUNCTIONAL UNIT REGENERATION VIA DENTAL FOLLICLE STEM CELLS* and *THERAPEUTIC POTENTIALS OF DENTAL FOLLICLE STEM CELLS IN NEUROLOGICAL DISEASES*.

5. *Bacterial infections have been reported to play a key role in the development of dental pulp necrosis (PMID: 34597722). Please*

emphasize this information

Response: Thanks for your good advice. We have added related content to this part. Please see underlined sentences in *Dental pulp necrosis and pulp regeneration* part (page 9).

6. *In case, when clinical trials are mentioned, the clinicaltrials.gov ID should be included*

Response: Thanks for your kind advice. We have added the Identifiers followed the clinical trials. Please see underlined sentences in *Periodontitis and periodontal regeneration* part (page 9).

7. *General comment, when the studies mentioned have been conducted with animal models, its should be underlined, as the biological/clinical information is more robust in this such of studies than in vitro studies.*

Response: Thanks for your kind advice. In general, clinical results are more robust than preclinical results, and preclinical animal model results are more robust than in vitro studies. In this manuscript, most of the results are based on preclinical animal models. More clinical trials of DFSCs should be performed in the future.

8. *“IMMUNOREGULATION OF DFSCS” acronyms should be avoided in the subhead titles*

Response: Thanks for your kind advice. We have modified all the subtitles that include acronyms.

9. “*CONCLUSION AND PERSPECTIVE*” better “*CONCLUSION AND FUTURE PERSPECTIVE*”

Response: Thanks for your kind advice. Once we had changed the subtitle to *CONCLUSION AND FUTURE PERSPECTIVE*, we later discovered that the editorial office had requested a unified first-level heading title as *CONCLUSION*. So, we changed it to *CONCLUSION*.

Reviewer: 2

Comments to the Author

This review focuses on the properties, application potential, and clinical transformation value of dental follicle stem cells (DFSCs) in oral and neurological diseases. This is an interesting review while some major defects caused my concerns. Unless the authors could solve these concerns, I would not suggest this manuscript to be considered publication in World Journal of Stem Cells.

Major concerns:

1、 The authors should supplement more details about the specific mechanism of DFSCs treatment for each disease. For example, lps-preconditioned DFSCs-derived small extracellular vesicles can treat periodontitis via reactive oxygen species/mitogen-activated protein kinase signaling-mediated antioxidant effect. (doi: 10.2147/IJN.S350869)

Response: Thanks for your kind suggestion. Microinflammation preconditioning is important to improve the regeneration and immunoregulation capacity of DFSCs and their secreted exosomes. We have added the related content to the manuscript. Please see underlined sentences in *Periodontitis and periodontal regeneration* part (page 8-9).

2、 In the Periodontitis and periodontal defects part and Dental pulp necrosis Part, the description of the scaffold takes up a long space. I cannot judge whether the DFSCs will not have these functions without the scaffold. The authors should separate the examples of whether or not

scaffolds are used into two paragraphs.

Response: Thanks for your kind suggestion. Stem cells, scaffold and growth factors (growth signals) are three core elements of tissue engineering. Scaffold plays a critical role in tissue engineering, providing support for transplanted stem cells and enhancing the therapeutic effects of tissue regeneration. The cell sheet technique prevents extracellular matrix degradation, which provides numerous growth factors and provides support to the cells. The extracellular matrix become the natural scaffold. Therefore, we paid more attention to clarified the importance of scaffold and cell sheets in periodontal and pulp regeneration.

3、*The authors list “Tooth root and whole tooth regeneration ” in the category of ORAL DISEASES, which is less suitable in my view. They should reconsider a different classification. For example, the Application in oral cavity can be classified as periodontal regeneration, pulp regeneration, root regeneration and whole tooth regeneration.*

Response: Thanks for your kind suggestion. We have modified the names of category. please see the subtitles in *ORAL DISEASES AND FUNCTIONAL UNIT REGENERATION VIA DENTAL FOLLICLE STEM CELLS* and *THERAPEUTIC POTENTIALS OF DENTAL FOLLICLE STEM CELLS IN NEUROLOGICAL DISEASES* parts.

4、 *In the IMMUNOREGULATION OF DFSCS part, the authors think “Both in oral and neurological diseases, the immunomodulatory capacity is one of the most crucial functions of MSCs to facilitate the repair or regeneration of damaged tissues.” . However, none of the examples cited later is in oral and neurological disease, nor does it illustrate the relationship between immunomodulatory capacity and repair or regeneration of damaged tissues in oral and neurological diseases. The author needs to consider the review content of this paragraph more carefully.*

Response: Thanks for the good advice. We have already added the references in the first sentence. At the same time, the aim of this section is to clarify that DFSCs also exhibit immunomodulatory capacity in other diseases.

5、 *The authors may also need to think about the length of the manuscript, for example the introduction of stem cells and mesenchymal stem cells in the first four paragraphs should be more concise in my view.*

Response: Thanks for the kind advice. This manuscript is a comment review required and defined by the editorial office; Therefore, we focus more on describing the background and introducing the topic in the *INTRDUCTION* section.

6、 *The part of CRYOPRESERVATION OF DFSCS is not reflected in the abstract.*

Response: Thanks for your good suggestion. We have added the part of cryopreservation of DFSCs in the *Abstract* part. Please see underlined sentences in *Abstract* part (page 3).

7、 *The picture is few and unattractive, so two or three summary pictures or tables should be added appropriately.*

Response: Thanks for your good suggestion. We have provided another figure to illustrate the mechanism and strategies of DFSCs based therapy in oral and neurological diseases. Please see Figure 2.

Minor concerns:

8、 *The author should pay attention to the citation format of the references in the article, such as the superscript of reference [22] in the last paragraph of the Introduction part.*

Response: Thanks for your kind suggestion. We have checked and modified all the format of references in this manuscript.

9、 *There is lack of references in the part about DFSCs in the treatment of PD between reference [79] and [81, 82].*

Response: Thanks for your kind suggestion. We have added the lack of

reference [99].

10、 All abbreviations need to have a full name, such as BCOR, PBMCs, ADSCs, UCMSCs and so on.

Response: Thanks for your kind suggestion. We have added the full name of these abbreviations when it appeared for the first time.