

2020/05/01

Dear Editor in-chief,

Thank you very much for the professional and kind comments on our paper, which was invited for submission to World Journal of Stem Cells (ID: 02456599). According to comments of all reviewers, we have carefully revised the manuscript. The revised parts have been marked in red in the revised paper. Please check the following details point by point.

Reviewer 1:

While the manuscript addresses a valuable scientific challenge and the potential of mesenchymal stem cells and mesenchymal stem cell-derived extracellular vesicles for treatment of rheumatic disease; the manuscript was submitted as a systematic review, however, although the authors submitted the PRISMA checklist, the items of the list are not reflected in the manuscript. The manuscript is not presented as a systematic review. There is no flow chart, the PICOS question is not demonstrated, the authors mention that there is a protocol registration number but it is not mentioned in the text neither are eligibility criteria, nor the search strategies used, nor the statistical analysis of the studies retrieved from the search, risk of bias is not mentioned, there are no tablesetc. In short, the manuscript does not fit the criteria of a systematic review but a narrative review at best with some valuable information to the scientific community.

Response to Reviewer 1: Thank you for the professional and kind comments on our article. We have carefully revised the paper according to your advice. Please check details as follows. Thank you very much.

Major issues:

1. There is no flow chart, the PICOS question is not demonstrated, the authors mention that there is a protocol registration number but it is not mentioned in the text neither are eligibility criteria, nor the search strategies used, nor the statistical analysis of the studies retrieved from the search, risk of bias is not mentioned, there are no tablesetc. In short, the manuscript does not fit the criteria of a systematic review but a narrative review at best with some valuable information to the scientific

community.

Response to point 1: Thank you for the professional comment on this point. We have revised the format of work in accordance with the standard requirements of the systematic review, added flow chart, eligibility criteria, the search strategies, statistical analysis...etc. In addition, we supplemented the relevant contents of the retrieval process in accordance with the principles of PICOS. We are sorry that we mistakenly wrote the protocol registration number in the text. Relevant content were added in text and marked in red. Please check details in the revised paper.

Reviewer 2:

This paper discusses the potential use of MSCs and MSC-EVs in treatment of rheumatic diseases. The subject is interesting and of relevance, however, the review repeats much of what has already been published and reviewed surrounding MSCs and more care should be given to link the literature to the disease states mentioned. The review is through but there are some additional points that should be covered.

Response to Reviewer 2: Thank you very much for the high appreciated and professional comments on our paper. We have carefully revised the paper based on your suggestions. Please check details as follows point by point.

Minor problems as followed:

1. how MSCs and/or EVs could be delivered as a treatment for rheumatic disease (e.g. systemically) and the source of the MSCs (bone marrow/adipose/other) and how this could affect the final treatment?

Response to point 1: Thank you very much for the kind reminding about this point. The effects of various administration route and tissue source of MSCs to the therapeutic action have been listed in section of discussion. The revised parts have been marked in red. Please check details in the revised paper. Thank you very much again.

2. The different information and studies given in the text could lend themselves to more tables and/or figures to ease the clarity of reading.

Response to point 2: Thank you very much for the kind reminding. We have added a figure (Fig.3) in the text. Thank you very much again.

3. The authors should consider changing the title to” Mesenchymal Stem Cell and Mesenchymal Stem Cell-derived Extracellular Vesicles: Potential Roles in Rheumatic Diseases” to reflect that these are not treatments that are currently available in clinic.

Response to point 3: Thank you very much for the kind comment on this point. We have changed the title to “Mesenchymal Stem Cell and Mesenchymal Stem Cell-derived Extracellular Vesicles: Potential Roles in Rheumatic Diseases”. Thank you very much again for this advice.

Reviewer 3:

This manuscript reviewed the roles of mesenchymal stem cells (MSCs) and mesenchymal stem cell-derived extracellular vesicles (EVs) in rheumatic diseases. The recent advances, functional roles and mechanisms of MSCs and EVs in rheumatic diseases are discussed. The work is interesting.

Response to Reviewer 3: Thank you very much for the high appreciated and professional comments on our paper. We have carefully revised the paper based on your suggestions. Please check details as follows point by point.

Minor problems as followed:

1. The authors should add one more paragraph at the end of introduction. In this paragraph, the authors should talk about the existing relevant reviews and the importance of current reviews. What make the current review different from the previous?

Response to point 1: Thank you very much for the kind reminding about this point. We have added one paragraph at the end of introduction with more words to summarize the previous work and explain the features of this work. The revised parts have been marked in red. Please check details in the revised paper. Thank you very much again.

2. The authors should add at least a figure to highlight several key studies discussed in the text.

Response to point 2: Thank you very much for the kind reminding. We have added a figure (Fig.4) in the text. Thank you very much again.

3. The authors should change the section of “Future directions” to “Conclusion and

future perspectives”. More points should be added to future perspectives with detailed explanations.

Response to point 3: Thank you very much for the kind reminding about this point. “Future directions” has been corrected as “Conclusion and future perspectives”, and we have polished the future perspectives section to be more detail. The revised parts have been marked in red. Please check details in the revised paper. Thank you very much again.

4. Figure 1, full form of all abbreviations should be stated in figure caption

Response to point 4: Thank you very much for the kind comment on this point. We have stated the full form of all abbreviations in all figure caption. Thank you very much again for this advice.

5. References should be added to Table 1.

Response to point 5: Thank you very much for the kind comment on this point. References have been added to Table 1. Thank you very much again for this advice.

6. The authors should cite and discuss some relevant publications which include but not limited to the followings: (a) Mesenchymal stem cells for regenerative medicine. Cells, 8(8), 886, 2019 (b) Mesenchymal stem cell therapy for ischemic tissues. Stem cells international, 2018. (c) Mesenchymal stem cell-based therapies in regenerative medicine: applications in rheumatology. Stem cell research & therapy, 2(2), 14, 2011.

Response to point 6: Thank you very much for the kind comment on this point. The publications listed above and others have been cited and discussed in the text. Special thanks to you for your good comments.

Thank you very much again for the professional and kind comments on the article. The manuscript has been carefully revised. Given the great contributions of Dr. Fengxia Liu, all authors have approved to add her as a co-author in the revised paper. If there are any other questions, please contact us by email as soon as possible.

Best regards,

Jinghan Yang et al.