July 10, 2020

Dear editors:

Thank you for your decision letter for manuscript #57148.

We here submit our revised manuscript entitled as "Senescent mesenchymal stem/stromal cells and restoring their cellular functions" for your consideration. We have revised the manuscript according to the comments in our capacity. The modified part in the manuscript has been marked in red for your information. We also enclose a point-by-point response letter to the suggestions of the reviewers and hope our answers have provided convincing information to them.

I would like to declare on behalf of my co-authors that the work has not been published previously, and not under consideration for publication elsewhere. No conflict of interest exits in the submission of this manuscript, and the manuscript is approved by all authors for publication.

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(On behalf of co-authors)

Reference： Manuscript # 57148

Title：Senescent mesenchymal stem/stromal cells and restoring their cellular functions

Reviewer #1:

1) First, I would pose a semantic question: should we still use the term 'transplantation' when referring to MSC therapeutic use? In my opinion, this word leads to a misinterpretation of this kind of therapy. Indeed, despite the use of stem cells, the effect is completely different from that intended for bone marrow transplantation (correct use). The difference lies in the fact that bone marrow transplantation is a once-in-a-life treatment and results in the reconstitution of the hematological compartments, including the immune system. By contrast, MSC administration represents a novel immunotherapy and not a kind of transplantation since they do not stably engraft in patients, but aid the target organ to overcome the injury while modulating the peripheral immune response. Therefore, I suggest to replace the term "MSC transplants" with "MSC administration".

Answer: Thank you for valuable suggestion. We totally agreed with that "MSC administration" is a more scientific terminology. We have replaced the "MSC transplants" with "MSC administration" or "MSC infusion" in the revised manuscript.

2) The title should be changed as follows: "Senescent mesenchymal stem/stromal cells and restoring their cellular functions".

Answer: Thank you for the valuable suggestion. We have changed the title as "Senescent mesenchymal stem/stromal cells and restoring their cellular functions" according to the reviewer suggested.

3) Please introduce a reference where the criteria for MSC definition are stated (Dominici M., et al. Cytotherapy 2006).

Answer: Sorry for not providing the relative information. The mentioned reference and the criteria for MSC definition has been added in the revised manuscript (Reference 1). (Page 4)

~~4)~~ Please, introduce a comment on the possible genetic instability of senescent MSC.

Answer: Thanks for the valuable suggestion. According to the Reviewer's suggestion, we have commented the genetic instability in senescent MSCs in Part 1.2 (Alterations of activity) and marked in red in the revised manuscript. (Page 6)

5) Why the short paragraph at the end of page 7 is highlighted in yellow?

Answer: Thank you very much for your careful reading. We are very sorry for our incorrect marker and have removed it.

6) In each section, the authors are jumping from human and mice results that jeopardize the message. Please, re-organize the paragraphs accordingly.

Answer: Thanks for the valuable suggestion. We have carefully read through the manuscript and re-organized part 1.4.1 in which the results of human and mice seemed disordered. In the revised manuscript, the changes of transcriptomics were described according to different tissue source of MSCs. We hope the revised manuscript will better meet the reviewer's expectations. (Page 8)

7) A note of caution on the possible clinical translation of the evidence presented should be added since they are collected mostly in *in vitro* studies.

Answer: Thanks for the valuable suggestion. We have added the relative content as suggested at the end of Part 2 in the revised manuscript. The added part is as follows: "The rejuvenation methods mentioned above have potentials to optimize the functional status of aged MSCs. However, most of them were *in vitro* or rodent model studies. Further research is needed to evaluate their long-term safety and efficacy before it can be clinically useful." (Page 21)

8) Please replace the word 'impired' with 'impaired' on page 13.

Answer: Sorry for the writing mistake and thanks for your patience and careful reading. The typo has been corrected in the revised manuscript.

9) Please explain the acronyms when used the first time. Avoid abbreviations when the term is used less than three times.

Answer: Thank you for your careful reading and professional suggestions. We have read through the manuscript and deleted the abbreviations used less than three times in the revised manuscript.

10) Please insert page numbers at the bottom of the pages.

Answer: Thank you for your suggestion. We have inserted the page numbers at the bottom of the pages.

Moreover, we have read through the manuscript made some additional changes. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper. Once again, thank you very much for your comments and suggestions.