

ROUND 1

Point-by-Point Responses to Reviews

Reviewer 1:

-----1. The author has spoken on human embryonic stem cells, or iPSC, and those doesn't mention in title so, the title should be improved.

-----Response: Thank you so much for reviewing our manuscript. We accepted the reviewer's suggestion and have revised the title of our manuscript.

-----2. Write how we enhance amount of EVs produced

-----Response: Thank you so much for reviewing our manuscript. We accepted the reviewer's suggestion and have discussed this topic in chapter 3.

Reviewer 2:

-----1. The review considers not only EVs derived from MSCs, but also from cells of other types and origin, so the title of the review should be rephrased.

-----Response: Thank you so much for reviewing our manuscript. We accepted the reviewer's suggestion and have revised the title.

-----2. Chapter 1.2, devoted to EVs isolation, should be expanded and discuss in more detail the existing methods for EVs isolation, including those induced, for example, using cytochalasin B, and discuss the advantages and limitations of currently existing methods.

-----Response: Thank you so much for reviewing our manuscript. We accepted the reviewer's suggestion and have discussed the advantages and limitations of currently existing methods in chapter 1.2.

----3. Chapter 3 I would also recommend slightly expanding and discussing in more detail, because it is a kind of quintessence of the whole review. In addition, it would be better if the authors make the conclusion in a separate chapter and expanded it a little.

-----Response: Thank you so much for reviewing our manuscript. We accepted the reviewer's suggestion and have discussed expanding in chapter 3. We have also made the conclusion in a separate chapter 4 in our manuscript.

----4. *Bibliography should be expanded. Some key publish are missed, such as: doi: 10.3389/fnins.2019.00163 doi: 10.3390/biology11121853 doi: 10.4103/1673-5374.266908*

-----Response: Thank you so much for reviewing our manuscript. We accepted the reviewer's suggestion and have revised in our manuscript.

-----5. *a) Unify the formatting of links in the text. It must be has space after the main text, for example: «Text [1].» b)The same is for links to Figures and Tables, for example: «Text (Fig.1).» c) Unify text formatting, in particular text alignment. d) Page 2. – Keywords: «... Cell-free stragegy» - typo, strategy*

keywords

-----Response: We are sorry for the spelling mistake and incorrect formatting in the manuscript and we have revised in our manuscript.

Reviewer 3:

----1. *Abstract: “Cell/stem cell-based therapies have made huge progress in tissue regeneration medical engineering. However, cell transplantation therapy has certain limitations including immune rejection and limited cell viability, which seriously hinder the transformation of stem cell-based tissue regeneration into clinical practice. Mesenchymal stem cells (MSCs) derived extracellular vesicles (EVs) not only possess the advantages of its derived cells, but also can avoid the risks of stem cells. MSCs-derived EVs are intelligent and controllable biomaterials that can participate in a variety of physiological and pathological activities, tissue repair and regeneration by transmitting a variety of biological signals, showing great potential in cell-free tissue regeneration.” is an overly lengthy introduction of EVs produced from mesenchymal stem cells. The abstract should be revised to include the highlights of this article.*

-----Response: Thank you so much for reviewing our manuscript. We accepted the reviewer's suggestion and have revised the abstract to include the highlights of this article in our manuscript.

----2. *Keywords: "Cell-free stragegy" should be Cell-free strategy.*

-----Response: We are sorry for the spelling mistake in the manuscript and we have revised in our manuscript.

----3. *Most of the references are too old. The studies published in 2021 and 2022 should be more reference-heavy.*

-----Response: Thank you for your kind advice and we have added several newly published studies in our manuscript.

----4. *Part "1. EVs ...". "Signals are communicated through vesicle membrane proteins or by vesicle contents such as mRNA." This sentence would be better if the vesicle contents were proteins, miRNAs, or lncRNAs.*

-----Response: Thank you for your kind advice and we have revised in our manuscript.

----5. *Part "2. Repair and regeneration effects of EVs ": The authors simply list the EVs of stem cells in various organs or tissues. It should be better to have some condensed discussion. The function of various EV contents should be discussed in the article. This will be interesting.*

-----Response: Thank you so much for reviewing our manuscript. We accepted the reviewer's suggestion and have listed several contents of EVs in Part 2.

----6. *Part 2.3&2.5: Human embryonic stem cells, or iPSC, are not part of the mesenchymal stem cells mentioned in the title. Therefore, the title should be improved.*

-----Response: Thank you so much for reviewing our manuscript. We accepted the reviewer's suggestion and have revised the title.

----7. *This article should be revised to present it in a better logical way.*

-----Response: Thank you for your kind advice and we have revised in our manuscript.

ROUND 2

Point-by-Point Responses to Reviews

---1. This article has been nicely revised. Before publication, the references should be cited in Table 1.

---Response: Thank you so much for reviewing our manuscript. We accepted the reviewer's suggestion and have revised our manuscript.

---2. Please provide fund documents, otherwise "Health Commission of Sichuan Province (21PJ062)." will be deleted

---Response: The documents have been attached in our email.

---3. For all reference formats, please refer to the first one, list all authors, and complete PMID and DOI. If there is no PMID and DOI, please provide the website

---Response: The reference formats have been revised in our manuscript.

---4. Your manuscript has been checked by CrossCheck. Please read the attached CrossCheck report for details. Similar sentences with other articles (highlighted in the CrossCheck Report), please rephrase these sentences. Our editorial policy states the overall similarity should be less than 30%, the overlapped section should be less than 5% in single papers, including author's own work. Please modify on the basis of the attached manuscript.

---Response: The similar sentences have been revised in our manuscript.