



PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 86992

Title: How to enhance the ability of mesenchymal stem cells to alleviate intervertebral disc degeneration

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer’s code: 05817547

Position: Peer Reviewer

Academic degree: PhD

Professional title: Postdoctoral Fellow

Reviewer’s Country/Territory: United Kingdom

Author’s Country/Territory: China

Manuscript submission date: 2023-07-17

Reviewer chosen by: Geng-Long Liu (Quit 2023)

Reviewer accepted review: 2023-08-04 10:13

Reviewer performed review: 2023-08-16 10:33

Review time: 12 Days

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input checked="" type="checkbox"/> Grade D: No creativity or innovation



Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

In this manuscript, the authors have evaluated “How to enhance the ability of mesenchymal stem cells to restore intervertebral disc degeneration”. Overall, this manuscript provides valuable data. There are some points, that I think are necessary for publishing the manuscript in maximum impacts. 1-The manuscript must be carefully proofread for grammar, spelling, and punctuation issues. 2-Despite similar phenotypes and the common mechanisms of tissue regeneration, the source of MSCs can play a crucial role in their therapeutic effects. Studies have shown that diversity in the microenvironment of MSCs and, subsequently, the expression of different genes lead to differences in their function and behavior. So, it has been suggested that tissue matched MSCs may increase the efficacy of their regenerative effects. Is there any difference between MSCs from different sources to restore intervertebral disc degeneration? It is recommended that describe it briefly. 3-If there are clinical studies or commercial products based on MSCs to restore intervertebral disc degeneration, it is recommended that mention it briefly.



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Peer-review model: Single blind

Reviewer's code: 04022623

Position: Peer Reviewer

Academic degree: PhD

Professional title: Adjunct Professor, Surgeon, Surgical Oncologist

Reviewer's Country/Territory: Spain

Author's Country/Territory: China

Manuscript submission date: 2023-07-17

Reviewer chosen by: Geng-Long Liu (Quit 2023)

Reviewer accepted review: 2023-08-08 21:32

Reviewer performed review: 2023-08-16 20:13

Review time: 7 Days and 22 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Firstly, I would like to congratulate you by the high quality of the submitted paper. The information provided has a highly potential clinical relevance. Maybe I would like you to develop more deeply some aspects in your paper. In the following sections, aspects I consider modifiable or revisable of the submitted manuscript will be highlighted. A section about the strengths and limitations of the presented minireview, or a paragraph, must be added to the end of the paper. In the TITTLE: I suggest changing the word “restore” to “alleviate”, because Stem Cells have not yet proven to “restore” the ID to its original state. In the ABSTRACT: • When authors say “...SCs has achieved good efficacy...” I think it can be better explained with a different word as “acceptable” or “promising”. And the best way could be to add some indicative data such as “improving pain in 10-30% cases”, “improving histology in animal models” (invented data), etc. based on the data from a previous review on the issue. • In the last sentence, they say “We provide new approaches...”, better written as “we provide a review of new approaches...” because not all the revised research is produced by the authors. In the INTRODUCTION: • Maybe the authors, although it is not a requisite for mini-reviews,



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Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

could add a paragraph explaining the methodology, if exist, for the review or criteria employed to select the references employed. In the miRNA IN EXOSOMES section, we can mention:

- Page 4, first line. Authors speak about Bone Marrow Stem Cells. What kind of cells do they refer to? Mesenchymal? Hematopoietic? Both?
- Later they speak about m-5p transport. The relation between this transport and miRNA, the title of this section, must be explained...
- In the last paragraph the abbreviation IVD appears... This abbreviation has not been presented before... Does it refer to Intervertebral Disc?

SPECIAL GENETIS AND MSCs: • Maybe genetics is better than genetis?

METABOLITES AND MSCs: • “Under the action of urolidin UA, urolidin UA was able”, maybe the writing is repetitive and the first “Under the action of urolidin UA,” is not necessary.

- Two sentences later: “These changes activates...” I am not able to understand to which changes refer the authors... They speak about urolidin UA and urolisene UA... Are they contained in MSCs exosomes? How are they linked to MSCs or exosomes?
- Last sentence: what are the supposed mechanisms of MSC exosomes to control reactive oxygen species (ROS) and malondialdehyde levels?

GEL-LOADED MSCs: • Page 6, second sentence. “...delivering vasorin... while releasing vasorin...” Is this a mistake or it is confounding the writing because it seems a different molecule is going to be mentioned the second time... • Also, the sentence containing the words of the previous commentary is very very long and difficult to follow and understand completely. Maybe it could be broken in different sentences to make it better understandable.

CURCULAR RNA AND EXOSOMES: • The title has a mistake: it is written CURCULAR instead of CIRCULAR.

- Third line: CAHM has not been presented before if it is an acronym and must be explained the first time it appears (probably Colorectal Adenocarcinoma HyperMethylated).

MSC MIXTURE: • This section begins with the following sentence: “MSC therapy alone has been shown to be effective for IDD, but its efficacy still falls short of expectations”. I believe that this issue



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needs to be analysed deeply with a brief paragraph, maybe at the beginning of the paper, reflecting the most relevant results of MSC therapy alone, based on one or more of the most relevant review articles on the field. As an example, doi: 10.1177/2192568219829024. The section “harsh environment of the ID” starts with a similar sentence that has an associated reference (number 49). I believe it could be the best to add a section at the beginning of the mini-review explaining briefly published results with MSCs alone, not as good as expected, and then to present the systems employed to enhance MSCs. •

Page 9, the sentence “Previous studies have found that collagen can promote differentiation of MSCs”. I think it is better to reinforce this message with at least one literature cite. STIMULATION INDUCTION WITH MSCs MIXTURE: • I have found nothing to comment. HARSH ENVIRONMENT OF THE ID: • Page 12, last paragraph: authors speak about LI and ROS, two abbreviations that have not been presented before, so they must explain their meaning the first time they appear. FUTURE DIRECTIONS: • This is one of the most important sections of the review. I believe that with the huge effort and research performed by the authors, they could add many more information and maybe some new ideas to this section. In my opinion, this section must be longer and have more information about “future” and not speak again of the presented information. MORE SUGGESTIONS OR GRAMMAR MODIFICATIONS: see in attached Word document with MS Word Control changes. Newly I would like to congratulate authors for their work. Keep working in this way and trying to publish your research.



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Reviewer's code: 03671246

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Thailand

Author's Country/Territory: China

Manuscript submission date: 2023-07-17

Reviewer chosen by: Geng-Long Liu (Quit 2023)

Reviewer accepted review: 2023-08-06 15:36

Reviewer performed review: 2023-08-17 06:30

Review time: 10 Days and 14 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

1. The title did not reflect the contents of the manuscript. Huge sections were dedicated to exosomes and micro RNA. 2. The preparation of MSCs in matrices and their unique properties should be summarized as a table. Their frequency of administration, adverse reactions, and cell fates at specified times should be included. 3. The route / location of administration should be included. The concerns for vasculature and compression pressure should be clearly explained. 4. A section regarding allogeneic MSCs should be included. 5. How about improving indigenous MSCs or tissue stem cells instead of injecting exogenous MSCs / exosomes? 6. All miRNAs / lncRNA, and cytokines should be compiled as their respective tables.



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Peer-review model: Single blind

Reviewer's code: 03671246

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Thailand

Author's Country/Territory: China

Manuscript submission date: 2023-07-17

Reviewer chosen by: Xin-Liang Qu

Reviewer accepted review: 2023-09-16 12:39

Reviewer performed review: 2023-09-25 06:00

Review time: 8 Days and 17 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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160, Pleasanton, CA 94566, USA
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E-mail: bpgoffice@wjgnet.com
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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

I have re-reviewed the manuscript and found its content acceptable.