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PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 76783

Title: Intratracheal Administration of Umbilical Cord-derived Mesenchymal Stem Cells Attenuates Hyperoxia-induced Multiple Organ Injury via HO-1 and JAK/STAT Pathways

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05818012
Position: Peer Reviewer
Academic degree: MD
Professional title: Doctor
Reviewer's Country/Territory: China
Author's Country/Territory: China

Manuscript submission date: 2022-03-30

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-04-01 12:01

Reviewer performed review: 2022-04-06 16:01

Review time: 5 Days and 4 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection

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Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

In this study, the authors systematically demonstrated that intrattracheal huc-Mscs administration can improve hyperoxia-induced lung, heart, and kidney injury by activating HO-1 expression and JAK/STAT3 signaling pathway, providing a new intervention approach for the treatment of multiple organ injury in premature infants in hyperoxia environment. Although the content is already very rich and comprehensive, I would like to make some important suggestions on some basic issues to help authors improve the quality of their current manuscripts. Major concerns: 1. Security aspects of testing. Potential hypersensitivity reactions from xenoanimal protein and double antibody cultures of mesenchymal stem cells are possible. Attention should be paid to whether there are related adverse reactions during the test. How to ensure the safety of the experiment? How to rule out that the increase in BALF protein in the test is not a result of hypersensitivity? 2. Why choose 4*10^5 cells instead of more or less? Is there any relevant comparative data to support. 3. How to determine a perfusion of 40 microliters, rather than more or less, without causing associated bronchial reactions and how to ensure the safety of the test. 4. Please try to detail the procedure of endotracheal administration of mesenchymal stem cells in rat models.

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05817451
Position: Peer Reviewer
Academic degree: MD
Professional title: Doctor
Reviewer's Country/Territory: Japan
Author's Country/Territory: China

Manuscript submission date: 2022-03-30

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-04-04 01:30

Reviewer performed review: 2022-04-14 02:37

Review time: 10 Days and 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection

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Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Name of Journal: World Journal of Stem Cells Manuscript NO: 76783 Intratracheal Administration of Umbilical Cord-derived Mesenchymal Stem Cells Attenuates Hyperoxia-induced Multiple Organ Injury via HO-1 and JAK/STAT Pathways General comments. This study examined the effects of human UC-MSCs on the lung, heart, and kidney using an animal model of hyperoxia-induced multiple organ injury. The results of histological morphology and quantitative evaluation of gene and protein expression in each organ suggest a positive effect of cell administration on the disease, and it is clinically significant that intratracheal and intraperitoneal routes of cell administration were investigated. In addition, comprehensive gene expression analysis by RNA-seq and protein expression analysis focusing on specific pathways are being conducted to search for mechanisms. This research is concerned with the therapeutic effects of cell transplantation on important diseases and the elucidation of their mechanisms, and we believe that it reinforces the known results regarding the therapeutic effects. However, the results obtained regarding the mechanism of action are relatively superficial, and I believe that a more in-depth study is needed as a contribution to this field. There are several points that need to be improved for publication, including insufficient explanation and discussion of the results. Major concerns 1. Changes in HO-1 expression and JAK/STAT pathway have been shown to occur with UC-MSC treatment. However, we believe that evidence that these changes are involved in phenotypic changes is lacking. It may be necessary to confirm whether the phenotype is altered by stimulating or inhibiting these molecular pathways. At the very least, it would be

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essential to consider this in the discussion. 2. There is little explanation or discussion of the data in Figure 5. Since this is important data, please add a description that will help readers understand the data and a comparative discussion with previous reports. Also, there is no information on RNA-seq in METHOD. The number of samples used and the analysis method should be described sufficiently. 3. Figure 8 contains inaccuracies. For example, the changes in expression of IL-10 and other molecules should not be the same. Also, the description of DNA double helix is not clear. The relationship of the top row of cells and molecular groups to individual animals and organs is also unclear. Specific comments. Introduction 1.HO-1 and JAK/STAT pathway are abruptly focused in the results section. Since the focus is not based on the screening results in this study, it would be more helpful to the reader if a background description of the reason for the focus is provided in the introduction. Material and Methods 1. Is chondrogenic differentiation a result of planar culture or does it appear to be a result of pellet culture? 2. As mentioned above, RNA-seq should be mentioned. Figures 1. As mentioned above, Figure 8 needs improvement. Others This study uses a xenotransplantation technique, in which Human UC-MSCs are transplanted into rats without allogeneic transplantation. Although I believe that this technique is not uncommon in studies on UC-MSC transplantation, we think it would be better to describe the differences between allogeneic and xenogeneic transplantation and the reasons why we chose xenogeneic transplantation.