May 4, 2022

Shengwen Calvin Li & Carlo Ventura
Editors-in-Chief
World Journal of Stem Cells

RE: manuscript ID **[76783]**.

Dear Editor:

I, along with my coauthors, would like to resubmit the attached manuscript for publication in *World Journal of Stem Cells*, titled "**Intratracheal Administration of Umbilical Cord-derived Mesenchymal Stem Cells Attenuates Hyperoxia-induced Multiple Organ Injury *via* HO-1 and JAK/STAT Pathways**."
The paper was coauthored by Na Dong, Pan-Pan Zhou, Dong Li, Hua-Su Zhu, Ling-Hong Liu, Hui-Xian Ma, Qing Shi, Xiu-Li Ju.

We are thankful for the reviewers' constructive comments, which have helped us to considerably improve and clarify the manuscript. We have responded to each of the reviewer's comments in a point-by-point manner. In addition, we have provided a revised version of the manuscript with the related statements polished. We hope that the changes incorporated into the revised manuscript satisfactorily address the reviewers' concerns.

Thank you for your consideration. We sincerely hope our manuscript is now suitable for publication in your journal.

Sincerely,
Xiu-Li Ju
Department of Pediatrics, Qilu Hospital of Shandong University
No. 107 Wenhua West Road, Jinan 250012, Shandong Province, China.
Email: jxlqlyy@163.com

Review #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

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 essential to consider this in the discussion.

R: Thank you very much for your valuable comments. Previous studies have reported that HO-1 contributes to attenuating hyperoxia-induced pulmonary inflammation, arterial remodeling, right ventricular hypertrophy, and renal injury. For example, Luo YY *et al*[1] reported that overexpression of HO-1 induced by lipoxin A4 attenuated hyperoxia-induced injury in murine lung epithelial cells *in vitro*. Moreover, ZnPP-IX, a HO-1 inhibitor, reversed the lipoxin A4-imparted protection on cell viability. Dunigan-Russell, K *et al*[2] and Yang, G *et al*[3] generated neonatal HO-1 knockout (KO) mice, and their findings indicated that HO-1 contributes to the resolution of lung injury following acute hyperoxia exposure. Additionally, HO-1's inhibitory effect on postexposure oxidative cardiac injury and inflammatory responses in cardiomyocyte-specific HO-1 KO mice was confirmed by Suliman, HB *et al*[4]. Hu, CM *et al*[5] demonstrate that HO-1 also has a critical protective role in Ang II–induced myocyte hypertrophy, which was significantly reversed by tin protoporphyrin IX administration, a HO-1 inhibitor. The research of Detsika, MG *et al*[6] establish HO-1 as a key regulator to attenuate glomerular injury by using HO-1deficient rats or rats with HO-1 overexpression targeted to glomerular epithelial cells.

Moreover, increasing evidence suggests that the JAK2/STAT3 signaling pathway plays a key role in protection against pulmonary, cardiac, and renal injury. In a sepsis mouse model, the therapeutic effects of MSCs on lung injury were reversed when the JAK2/STAT3 signaling pathway was inhibited by the specific inhibitor or siRNA[7]. It's also reported that the JAK2/STAT3 signaling pathway involves in mediating protection against cardiac injury[8, 9]. The protective effects were further verified by using the selective inhibitor of JAK2/STAT3. A recent study by Liu, Y[10] confirmed that the activation of the JAK2/STAT3 signaling pathway conferred anti-oxidative stress and reno-protective effect, using renal injury rats treated with apigenin in the absence or presence of the JAK2-specific inhibitor or siRNA. Interestingly, the evidence demonstrated that cross-talk may exist between HO-1 and JAK/STAT pathways[11-13].

Our findings suggest that the infusion of hUC-MSCs into neonatal rats further enhanced HO-1 expression and activated JAK2/STAT3 signaling pathway in the lungs, heart, and kidneys. Following your precious suggestions, relevant studies demonstrating the relationship between HO-1 expression and activated JAK2/STAT3 pathway and the

phenotype of tissue-protective effects have been added to **DISCUSSION** (kindly see page 22 line 5-9 and line 24-29).

However, it's noteworthy that the involvement of specific pathways in the therapeutic phenotype of MSCs still warrants much research. In the present study, we speculated that the changes in HO-1 expression and activated JAK2/STAT3 pathways are involved in the therapeutic changes in phenotype based on previous studies. Further in-depth mechanistic studies will be needed to validate and understand the molecular mechanisms modulated by hUC-MSCs. We plan to delve into the details in the near future. Moreover, we have added the limitation of this study on page 23 line 22-27.

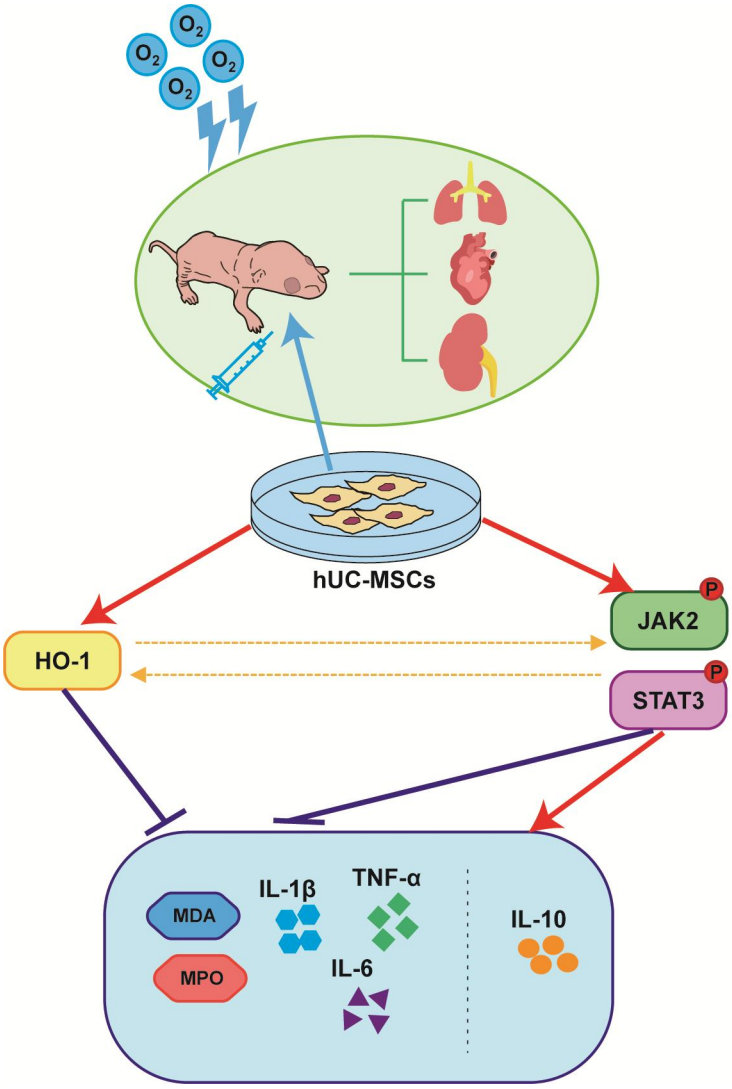
2. There is little explanation or discussion of the data in Figure 5. Since this is important data, please add a description that will help readers understand the data and a comparative discussion with previous reports. Also, there is no information on RNA-seq in METHOD. The number of samples used and the analysis method should be described sufficiently.

R: Thank you very much for your critical and useful comments. Following your valuable suggestions, the description of lung transcriptome sequencing results, including differentially expressed genes and gene ontology enrichment analyses was further enriched in **RESULTS** (kindly see page 17 line 6-22). Previous studies related to the transcriptome sequencing of BPD lung tissues have also been supplemented and compared in **DISCUSSION** (kindly see page 20 line 3-15). Moreover, we realized the deficiency of our experiment. Specifically, we only performed transcriptome sequencing of the whole-lung tissue, which consisted of several types of cells. Gene expression changes of sorted cell subtypes from multiple organs exposed to hyperoxia should be studied and validated in future research to assess the effect of MSCs on different target cell populations and address the underlying molecular mechanisms. The limitations and perspectives have been added to the end of the **DISCUSSION** (kindly see page 23 line 17-22). We apologize for ignoring the description of RNA-seq in the method. A detailed description regarding the method of RNA-sequencing and analysis has been added to **MATERIALS AND METHODS** (kindly see page 12 line 25-29 and page 13 line 1-9).

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.

R: Again, thank you for your valuable comments. In agreement with your precious suggestions, we have modified **Figure 8**, as shown below. Firstly, the changes in the expression of IL-10 were separated from other molecules. Secondly, the DNA double helix between HO-1 and JAK/STAT pathways was replaced by dotted arrows to demonstrate the possible cross-talk between the two pathways. Thanks to your critical prompting, the top row of cells and molecular groups to individual animals and organs were realized to be redundant and have been deleted in the revised **Figure 8**.



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.

R: Thank you very much for your valuable comment. HO-1 and JAK/STAT pathways were focused on in this study for their potent antioxidant, anti-inflammatory, and anti-apoptotic attributes in the development of pulmonary, cardiovascular, and renal diseases. In agreement with your valuable suggestions, we have added a background description of the reason for the focus on HO-1 and JAK/STAT pathways in the **INTRODUCTION** (kindly see page 7 line11-20).

Material and Methods:

1. Is chondrogenic differentiation a result of planar culture or does it appear to be a result of pellet culture?

R: Thank you very much for your valuable comment. To demonstrate the chondrogenic differentiation potential, hUC-MSCs were seeded in a loosely capped 15mL centrifuge tube (430790, Corning, NY, USA) and cultured in chondrogenic differentiation (HUXUC-90042, Cyagen) medium at 37 ℃ with 5% CO_2. The medium was changed every 3 days in accordance with the manufacturer's instructions. When the cell clusters were gathered, the cartilage balls were slightly ejected from the bottom of the centrifuge tube and continued to be induced and cultured at 37 ℃ with 5% CO_2. At the end of 21 days, the cartilage balls were fixed with 4% paraformaldehyde (PFA), embedded in paraffin, sectioned, and stained with alcian blue.

We apologize for the ambiguity made by inaccurate statements. Following your valuable suggestions, we have modified the method of chondrogenic differentiation induction in the revised manuscript (kindly see page 8 line 15-19).

2. As mentioned above, RNA-seq should be mentioned.

R: Thank you very much for your valuable comment. We apologize for this oversight. Following your kind suggestions, we have added a detailed description regarding the method of RNA-sequencing and analysis to **MATERIALS AND METHODS** (kindly see page 12 line 25-29 and page 13 line 1-9).

Figures: 1. As mentioned above, Figure 8 needs improvement.

R: Thank you very much for your valuable comment. Following your precious suggestions, we have modified **Figure 8**, as shown and described above.

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.

R: Again, thank you very much for your precious comment. In our study, the therapeutic effects of human UC-MSCs were investigated on hyperoxia-induced multiple organ injury. Human UC-MSCs are more attractive in cell therapies and regenerative medicine for the following reasons. Firstly, unlike stem cells harvested from other sources such as the bone marrow (BM-MSCs), adipose tissue(AD-MSCs), and endometrium, the human umbilical cord tissues are readily available in large quantities and its stem-cell derivatives are easily recovered without the donors incurring any invasive surgical procedures[14]. Secondly, lower immunogenicity and higher overall immunomodulatory effect with increased expression of potent immunosuppressive factors were observed for human UC-MSCs over BM-MSCs[15]. What's more, in vitro study showed that human UC-MSCs underwent slower senescence and demonstrated a higher cell proliferation rate and greater anti-inflammatory effects than BM-MSCs[16].

Notably, there are several studies confirmed that MSCs are poorly immunogenic. For example, Gutiérrez-Fernández, M et al[17] reported that both allogeneic rat adipose tissue-derived-mesenchymal stem cells (rAD-MSCs) transplantation and xenogeneic human AD-MSCs (hAD-MSCs) administration showed equal efficacy in terms of functional recovery and decreased ischemic brain damage without side effects or tumor formation. The research of Lin, KC et al[18] demonstrated that both xenogeneic and allogenic AD-MSCs protected the lung against ischemia-reperfusion injury via suppressing the inflammatory, oxidative stress, and autophagic signaling. What's more, xenogeneic hUC-MSCs transplantation had been extensively investigated over the past decades on various animal models with promising effects and no adverse events. Taken together, xenogeneic

hUC-MSCs transplantation was chosen in this study. As we anticipated, xenogeneic hUC-MSCs transplantation significantly alleviated the multiple organ injury induced by hyperoxia exposure with no related adverse reactions observed.

Following your kind advice, we have added a description regarding the additional advantages of hUC-MSCs, the differences between allogeneic and xenogeneic transplantation, and the reasons why we chose xenogeneic hUC-MSCs transplantation to the **INTRODUCTION** (kindly see page 6 line 29 and page 6 line 1-7). We sincerely hope that our responses are satisfactory for you to consider this article for publication.

Review #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

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?

R: Thank you very much for your valuable comment. Safety remains a primary issue in cell transplantation. Given the security of xenogeneic MSCs transplantation[17, 18] and

additional advantages of hUC-MSCs, such as higher isolation efficiency and proliferation capacity[14, 15], lower immunogenicity, and greater overall immunomodulatory and anti-inflammatory effects[16, 17], xenogeneic hUC-MSCs transplantation was chosen in our study. During the test, special attention was paid to whether there were adverse reactions to allogeneic transplantation. As we anticipated, our findings showed that xenogeneic hUC-MSCs transplantation significantly alleviated the multiple organ injury induced by hyperoxia exposure with no related adverse reactions observed.

Some efforts were made to ensure the safety of the experiment. Firstly, the hUC-MSCs were provided by the Cell and tissue bank of Shandong province (Jinan, China). The stringent safety assurance system with appropriate donor selection and screening as well as employing sensitive screening tests for infectious diseases is well equipped in the cell and tissue bank. Secondly, standardization in isolation protocols and culture conditions was rigorously controlled to reduce heterogeneity. Moreover, we closely monitored the symptoms and signs of neonatal rats before and after the transplantation of xenogeneic hUC-MSCs and prepared to deal with relevant adverse reactions in time.

Increasing evidence suggests that xenogeneic MSCs administration reduced the protein concentrations, the infiltration of neutrophils, and the levels of inflammation in BALF in mice or rat models[19-21]. In the study of Chang, YS et al[22], a comparison between the normoxia control group, normoxia + intraperitoneal human UC-MSCs group, and normoxia + intratracheal human UC-MSCs group was shown. The result demonstrated that xenotransplantation of human MSCs into immunocompetent wild-type rats did not result in any of the apparent gross or microscopic findings consistent with abnormal immunologic reactions. In our study, total protein levels in BALF were measured as an indication of endothelial and epithelial permeability. Hyperoxia-exposed animals demonstrated elevated BALF protein concentrations compared to normoxia-exposed pups, which was ameliorated by hyperoxia + xenogeneic hUC-MSCs administration (intratracheally or intraperitoneally). When the BALF protein concentration was compared with the normoxia group, there is no significant difference was observed in xenogeneic hUC-MSCs transplantation groups, both intratracheally and intraperitoneally. Based on the previous studies and our results, we safely demonstrated that ameliorated the hyperoxia-induced high permeability of the lung epithelium with no hypersensitivity reactions in this research.

2. Why choose 4*10^5 cells instead of more or less? Is there any relevant comparative data to support.

R: Thank you very much for your comment. The dose and volume of MSCs in our study were selected based on previous literature. In a comparative study by Chang, YS et al[23], three different doses of human UCB-derived MSCs, 5×10^3, 5×10^4, and 5×10^5, were delivered intratracheally in hyperoxia exposed neonatal rats. It's demonstrated that inflammatory responses and oxidative stress were significantly attenuated in both 5×10^4, and 5×10^5 groups but not in the 5×10^3 group. A meta-analysis[24] showed that a medium dose of 10^5–10^6 cells is the most widely used and has achieved remarkable therapeutic effects. In our study, 4×10^5 MSCs, a medium dose, were administrated to neonatal rats. At this appropriate dose, it is enough to obtain excellent therapeutic effects, without unnecessary waste and adverse reactions.

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.

R: Thank you very much for your useful comments. The perfusion volume is determined by the total number of MSCs used and cell density. Commonly, cell suspensions with a density of 1-1.5 $\times 10^7$ / mL are most frequently selected. The volume ranges from 20 μL to 50 μL has been proved to be safe for intratracheal transplantation, without causing associated bronchial reactions[22, 25-27]. According to the selected MSCs dose of 4×10^5 and the cell density of 1×10^7 / mL, the volume of 40 μL was chosen in our study.

To ensure the safety of the procedure of endotracheal administration, the following methods were taken. Firstly, the total cell number and volume of MSCs suspensions were selected legitimately. Secondly, a single cell suspension MSCs were prepared through a 30 μm filter before injection to avoid obstruction caused by cell aggregation. Furthermore, the rats were properly anesthetized before endotracheal intubation to avoid damage caused by their struggling movements and to minimize pain. Additionally, the operation of endotracheal intubation is guided by an experienced researcher. Ensure accurate and rapid action to reduce relevant airway damage. In the present study, all neonatal rats in the hyperoxia+ iT-hUC-MSCs group were successfully endotracheal intubated and

transplanted with MSCs. No mortality induced by the intratracheal administration procedure was observed.

4. Please try to detail the procedure of endotracheal administration of mesenchymal stem cells in rat models.

R: Thank you very much for your valuable advice. For intratracheal administration, the neonatal rats on P7 were euthanized via intraperitoneal injection of pentobarbital sodium and restrained on a board with the neck in hyperflexion. The 29-gauge needle syringe (320310, Becton, Dickinson and Company, NJ, USA) with the tip smoothened and wrapped with a 0.3 mm flexible capillary pipe was prepared as endotracheal intubation. The light source was placed close to the neck of the rat. The rat's tongue was wrapped and pulled outside the mouth with gauze in the right hand, the root of the tongue was gently pressed with a small tweezer to expose the glottis with the left hand. hUC-MSCs were transplanted into the trachea through the prepared endotracheal intubation at the glottis opening. Then the rats were allowed to recover from the anesthesia and return to their dam. Mortality induced by the intratracheal administration procedure was not observed. Following your kind suggestions, we have added a detailed description regarding the endotracheal administration of MSCs in rat models to **MATERIALS AND METHODS** (kindly see page 9 line 16-27). We sincerely hope our responses and the changes in the revised manuscript satisfactorily address your concerns.

Science editor:

The content of the manuscript could be interesting to WJSC readers. Several changes are suggested.

1. Please add details to your methods (and selection of them).

R: Thank you very much for your valuable comment. Following the kind suggestions from you and other reviewers, we have added a detailed description regarding endotracheal administration of mesenchymal stem cells in rat models (kindly see page 9

line 16-27), as well as RNA-sequencing and analysis (kindly see page 12 line 25-29 and page 13 line 1-9), to **MATERIALS AND METHODS**.

2. Discussion and conclusions should be enriched and clear.

R: Thank you very much for your comment. Following the kind suggestions from you and the reviewers, a detailed description and comparison regarding the transcriptome sequencing of BPD lung tissues have been added to the **DISCUSSION** (kindly see page 20 line 3-15). Relevant studies demonstrating the relationship between HO-1 expression and activated JAK2/STAT3 pathway and the phenotype of tissue-protective effects have also been added to the **DISCUSSION** (kindly see page 22 line 5-9 and line 24-29). The conclusions were also modified to make them clearer. Moreover, according to the comments of peer reviewers, the **INTRODUCTION** (kindly see page 6 line 29, page 6 line 1-7, and page 7 line11-20) and **RESULTS** (kindly see page 17 line 6-22) were also modified as mentioned above.

3. The limitations of your study and prospective studies are desirable in your discussion section.

R: Thank you very much for your comment. We acknowledge that there are several limitations to this study. Following your kind suggestions, the limitations and perspectives have been added to the end of the **DISCUSSION** (kindly see page 23 line 17-27). Furthermore, the related statements have also been polished. The revised manuscript has been uploaded. Thank you again for your scrutiny.

Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Stem Cells, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision

according to the Peer-Review Report, Editorial Office ' s comments and the Criteria for Manuscript Revision by Authors.

1. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, " Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...".

R: Thank you very much for your comment. Following your valuable suggestions, we have checked all the figure legends throughout and corrected the mistakes in the revised manuscript.

2. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

R: Thank you for bringing this point to our attention. We have added the original decomposable figures to a single PowerPoint file and uploaded the file as "76783-Figures.pptx" into the system.

3. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

R: Thank you for your reminder. Following your kind advice, we have added the "Copyright ©The Author(s) 2022" to the bottom right-hand side of all original pictures. Please see the PowerPoint file named "76783-Image File". We appreciate your diligence.

REFERENCES

1 Luo YY, Wu SH, Lu HY, Li BJ, Li SJ, Sun ZY, Jin R and Chen XQ. Lipoxin A4 attenuates hyperoxia-induced lung epithelial cell injury via the upregulation of heme oxygenase-1 and inhibition of proinflammatory cytokines. *Mol Med Rep* 2020; **21**: 429-437 [PMID: 31746387 DOI: 10.3892/mmr.2019.10821]

2 Dunigan-Russell K, Silverberg M, Lin VY, Li R, Wall SB, Li Q, Nicola T, Gotham J, Crowe DR, Vitiello PF, Agarwal A and Tipple TE. Club Cell Heme Oxygenase-1 Deletion: Effects in Hyperoxia-Exposed Adult Mice. *Oxid Med Cell Longev* 2020; **2020**: 2908271 [PMID: 32587658 DOI: 10.1155/2020/2908271]
3 Yang G, Biswasa C, Lin QS, La P, Namba F, Zhuang T, Muthu M and Dennery PA. Heme oxygenase-1 regulates postnatal lung repair after hyperoxia: role of β-catenin/hnRNPK signaling. *Redox biology* 2013; **1**: 234-43 [PMID: 24024157 DOI: 10.1016/j.redox.2013.01.013]
4 Suliman HB, Keenan JE and Piantadosi CA. Mitochondrial quality-control dysregulation in conditional HO-1(-/-) mice. *JCI insight* 2017; **2**: e89676 [PMID: 28194437 DOI: 10.1172/jci.insight.89676]
5 Hu CM, Chen YH, Chiang MT and Chau LY. Heme oxygenase-1 inhibits angiotensin II-induced cardiac hypertrophy in vitro and in vivo. *Circulation* 2004; **110**: 309-16 [PMID: 15226216 DOI: 10.1161/01.Cir.0000135475.35758.23]
6 Detsika MG, Duann P, Atsaves V, Papalois A and Lianos EA. Heme Oxygenase 1 Up-Regulates Glomerular Decay Accelerating Factor Expression and Minimizes Complement Deposition and Injury. *The American journal of pathology* 2016; **186**: 2833-2845 [PMID: 27662796 DOI: 10.1016/j.ajpath.2016.07.009]
7 Liu W, Gao Y, Li H, Wang H, Ye M, Jiang G, Chen Y, Liu Y, Kong J, Liu W, Sun M, Hou M and Yu K. Intravenous transplantation of mesenchymal stromal cells has therapeutic effects in a sepsis mouse model through inhibition of septic natural killer cells. *The international journal of biochemistry & cell biology* 2016; **79**: 93-103 [PMID: 27521657 DOI: 10.1016/j.biocel.2016.08.013]
8 Zhang L, Wang X, Zhang H, Feng M, Ding J, Zhang B, Cheng Z and Qian L. Exercise-induced peptide EIP-22 protect myocardial from ischaemia/reperfusion injury via activating JAK2/STAT3 signalling pathway. *Journal of cellular and molecular medicine* 2021; **25**: 3560-3572 [PMID: 33710777 DOI: 10.1111/jcmm.16441]
9 Qiao S, Mao X, Wang Y, Lei S, Liu Y, Wang T, Wong GT, Cheung CW, Xia Z and Irwin MG. Remifentanil Preconditioning Reduces Postischemic Myocardial Infarction and Improves Left Ventricular Performance via Activation of the Janus Activated Kinase-2/Signal Transducers and Activators of Transcription-3 Signal Pathway and Subsequent Inhibition of Glycogen Synthase Kinase-3β in Rats. *Critical care medicine* 2016; **44**: e131-45 [PMID: 26468894 DOI: 10.1097/ccm.0000000000001350]
10 Liu Y, Wang L, Du Y, Chen Z, Guo J, Weng X, Wang X, Wang M, Chen D and Liu X. Effects of apigenin pretreatment against renal ischemia/reperfusion injury via activation of the JAK2/STAT3 pathway. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie* 2017; **95**: 1799-1808 [PMID: 28962085 DOI: 10.1016/j.biopha.2017.09.091]
11 Tron K, Samoylenko A, Musikowski G, Kobe F, Immenschuh S, Schaper F, Ramadori G and Kietzmann T. Regulation of rat heme oxygenase-1 expression by interleukin-6 via the Jak/STAT pathway in hepatocytes. *J Hepatol* 2006; **45**: 72-80 [PMID: 16510205 DOI: 10.1016/j.jhep.2005.12.019]
12 Yan X, Cheng X, He X, Zheng W, Yuan X and Chen H. HO-1 Overexpressed Mesenchymal Stem Cells Ameliorate Sepsis-Associated Acute Kidney Injury by Activating JAK/stat3 Pathway. *Cellular and molecular bioengineering* 2018; **11**: 509-518 [PMID: 31719896 DOI: 10.1007/s12195-018-0540-0]

13 Lee PJ, Camhi SL, Chin BY, Alam J and Choi AM. AP-1 and STAT mediate hyperoxia-induced gene transcription of heme oxygenase-1. *American journal of physiology. Lung cellular and molecular physiology* 2000; **279**: L175-82 [PMID: 10893216 DOI: 10.1152/ajplung.2000.279.1.L175]
14 Chia WK, Cheah FC, Abdul Aziz NH, Kampan NC, Shuib S, Khong TY, Tan GC and Wong YP. A Review of Placenta and Umbilical Cord-Derived Stem Cells and the Immunomodulatory Basis of Their Therapeutic Potential in Bronchopulmonary Dysplasia. *Front Pediatr* 2021; **9**: 615508 [PMID: 33791258 DOI: 10.3389/fped.2021.615508]
15 Lu LL, Liu YJ, Yang SG, Zhao QJ, Wang X, Gong W, Han ZB, Xu ZS, Lu YX, Liu D, Chen ZZ and Han ZC. Isolation and characterization of human umbilical cord mesenchymal stem cells with hematopoiesis-supportive function and other potentials. *Haematologica* 2006; **91**: 1017-26 [PMID: 16870554]
16 Kern S, Eichler H, Stoeve J, Klüter H and Bieback K. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. *Stem cells (Dayton, Ohio)* 2006; **24**: 1294-301 [PMID: 16410387 DOI: 10.1634/stemcells.2005-0342]
17 Gutiérrez-Fernández M, Rodríguez-Frutos B, Ramos-Cejudo J, Otero-Ortega L, Fuentes B, Vallejo-Cremades MT, Sanz-Cuesta BE and Díez-Tejedor E. Comparison between xenogeneic and allogeneic adipose mesenchymal stem cells in the treatment of acute cerebral infarct: proof of concept in rats. *Journal of translational medicine* 2015; **13**: 46 [PMID: 25637958 DOI: 10.1186/s12967-015-0406-3]
18 Lin KC, Yeh JN, Chen YL, Chiang JY, Sung PH, Lee FY, Guo J and Yip HK. Xenogeneic and Allogeneic Mesenchymal Stem Cells Effectively Protect the Lung Against Ischemia-reperfusion Injury Through Downregulating the Inflammatory, Oxidative Stress, and Autophagic Signaling Pathways in Rat. *Cell transplantation* 2020; **29**: 963689720954140 [PMID: 33050736 DOI: 10.1177/0963689720954140]
19 Xiang B, Chen L, Wang X, Zhao Y, Wang Y and Xiang C. Transplantation of Menstrual Blood-Derived Mesenchymal Stem Cells Promotes the Repair of LPS-Induced Acute Lung Injury. *Int J Mol Sci* 2017; **18**: [PMID: 28346367 DOI: 10.3390/ijms18040689]
20 Feng B, Zhu J, Xu Y, Chen W, Sheng X, Feng X, Shi X, Liu J, Pan Q, Yang J, Yu J, Li L and Cao H. Immunosuppressive effects of mesenchymal stem cells on lung B cell gene expression in LPS-induced acute lung injury. *Stem cell research & therapy* 2020; **11**: 418 [PMID: 32977837 DOI: 10.1186/s13287-020-01934-x]
21 Niu H, Song H, Guan Y, Zong X, Niu R, Zhao S, Liu C, Yan W, Guan W and Wang X. Chicken bone marrow mesenchymal stem cells improve lung and distal organ injury. *Sci Rep* 2021; **11**: 17937 [PMID: 34508136 DOI: 10.1038/s41598-021-97383-4]
22 Chang YS, Oh W, Choi SJ, Sung DK, Kim SY, Choi EY, Kang S, Jin HJ, Yang YS and Park WS. Human umbilical cord blood-derived mesenchymal stem cells attenuate hyperoxia-induced lung injury in neonatal rats. *Cell transplantation* 2009; **18**: 869-86 [PMID: 19500472 DOI: 10.3727/096368909x471189]
23 Chang YS, Choi SJ, Sung DK, Kim SY, Oh W, Yang YS and Park WS. Intratracheal transplantation of human umbilical cord blood-derived mesenchymal stem cells dose-dependently attenuates hyperoxia-induced lung injury in neonatal rats. *Cell transplantation* 2011; **20**: 1843-54 [PMID: 23167961 DOI: 10.3727/096368911x565038]
24 Augustine S, Avey MT, Harrison B, Locke T, Ghannad M, Moher D and Thébaud B. Mesenchymal Stromal Cell Therapy in Bronchopulmonary Dysplasia: Systematic

Review and Meta-Analysis of Preclinical Studies. *Stem cells translational medicine* 2017; **6**: 2079-2093 [PMID: 29045045 DOI: 10.1002/sctm.17-0126]
25 Sutsko RP, Young KC, Ribeiro A, Torres E, Rodriguez M, Hehre D, Devia C, McNiece I and Suguihara C. Long-term reparative effects of mesenchymal stem cell therapy following neonatal hyperoxia-induced lung injury. *Pediatric research* 2013; **73**: 46-53 [PMID: 23138401 DOI: 10.1038/pr.2012.152]
26 Pierro M, Ionescu L, Montemurro T, Vadivel A, Weissmann G, Oudit G, Emery D, Bodiga S, Eaton F, Péault B, Mosca F, Lazzari L and Thébaud B. Short-term, long-term and paracrine effect of human umbilical cord-derived stem cells in lung injury prevention and repair in experimental bronchopulmonary dysplasia. *Thorax* 2013; **68**: 475-84 [PMID: 23212278 DOI: 10.1136/thoraxjnl-2012-202323]
27 Chou HC, Chang CH, Chen CH, Lin W and Chen CM. Consecutive daily administration of intratracheal surfactant and human umbilical cord-derived mesenchymal stem cells attenuates hyperoxia-induced lung injury in neonatal rats. *Stem cell research & therapy* 2021; **12**: 258 [PMID: 33933128 DOI: 10.1186/s13287-021-02335-4]