

Dear Editor and Reviewers,

We would like to thank the *World Journal of Stem Cells* for giving us the opportunity to revise our manuscript entitled “Interferon- γ priming enhances the therapeutic effects of menstrual blood-derived stromal cells in a mouse liver ischemia-reperfusion model via indoleamine 2,3- dioxygenase”. We appreciate all of the Reviewers’ comments and suggestions. Additionally, we thank the Science Editor and Reviewers for pointing out the issues with the English usage in our draft, and the editing certificate has been provided with the uploaded files. We have carefully considered and addressed the concerns raised by the reviewers and the editors. A summary of the revisions and responses is provided below.

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: The authors have written this manuscript on an interesting topic and a well-designed study. There are no major issues I can point to. **Minor comments: 1. Every figure should be independent and self-**

sufficient. Hence, it would be better to use the elaboration of the terms and proper explanation of the figures in the figure legends.

Response: Thank you very much. We have modified the figure legends and explained the terms and results in more detail. We hope that these changes help present our data in a clearer manner. We sincerely hope the revised manuscript will meet your requirements. Thank you!

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: **Grade B (Minor language polishing)**

Conclusion: Accept (General priority)

Specific Comments to Authors: Well conducted study with menstrual blood stem cells

Response: Thank you very much for your positive comments about our work. The English usage in our draft was polished by AJE, a reputable language polishing company, and the related proof has been provided with the uploaded files. We sincerely hope that the revised manuscript will meet the publication requirements (Grade A). Thank you!

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: **Grade B (Minor language polishing)**

Conclusion: Accept (General priority)

Specific Comments to Authors: Mesenchymal stem cells (MSCs) have been used in liver transplantation and have certain effects in alleviating liver ischemia-reperfusion injury (IRI) and regulating immune rejection. However, some studies have indicated that the effects of MSCs are not very significant. Therefore, approaches that enable MSCs to exert significant and stable therapeutic effects are worth further study. **AIM:** To enhance the therapeutic potential of human menstrual blood-derived stromal cells (MenSCs) in the mouse liver ischemia-reperfusion model via interferon- γ (IFN- γ) priming. **METHODS:** Apoptosis was analysed by flow cytometry to evaluate the safety of IFN- γ priming, and indoleamine 2,3-dioxygenase (IDO) levels were measured by qRT-PCR, western blotting, and ELISA to evaluate the efficacy of IFN- γ priming. In vivo, the liver ischemia-reperfusion model was established in male C57/BL mice, H&E and TUNEL staining was performed and serum liver enzyme levels were measured to assess the degree of liver injury, and regulatory T cell (Treg) numbers in spleens were determined by flow cytometry to assess immune tolerance potential. Metabolomics analysis was conducted to elucidate the potential mechanism underlying the regulatory effects of primed MenSCs. In vitro, we established a hypoxia/reoxygenation (H/R) model and analysed apoptosis by flow cytometry to investigate the mechanism by which primed MenSCs inhibit apoptosis. Transmission electron microscopy (TEM), western blotting, and immunofluorescence were used to analyse autophagy levels. **RESULTS:** IFN- γ -primed MenSCs secreted higher IDO levels, attenuated liver injury, and increased Treg numbers in mouse spleens to greater degrees than untreated MenSCs. Metabolomics and autophagy analyses proved that primed MenSCs more strongly induced autophagy in mouse livers. In the H/R model, autophagy inhibitors increased H/R-induced apoptosis, indicating that autophagy exerted protective effects. In addition, primed MenSCs decreased H/R-induced apoptosis via IDO and autophagy. Further rescue experiments proved that IDO enhanced the protective autophagy by inhibiting the mTOR pathway and activating the AMPK

pathway. CONCLUSION: IFN- γ -primed MenSCs exerted better therapeutic effects in the liver ischemia-reperfusion model by secreting higher IDO levels. MenSCs and IDO activated the AMPK-MTOR-autophagy axis to reduce IRI, and IDO increased Treg numbers in the spleen and enhanced MenSC-mediated induction of immune tolerance. Our study suggests that IFN- γ -primed MenSCs may be a novel and superior mesenchymal stem cell product for liver transplantation in the future. In General: it's a good paper and the subject of the manuscript is applicable and useful. Title: the title properly explains the purpose and objective of the article Abstract: abstract contains an appropriate summary for the article, the language used in the abstract is easy to read and understand, and there are no suggestions for improvement. Introduction: authors do provide adequate background on the topic and reason for this article and describe what the authors hoped to achieve. MATERIALS AND METHODS: - The variables selected for the study are described clearly and are appropriate, given the nature of the question asked. - The research design is described in detail. - The research design is appropriate and does not contain particular weaknesses. - The measurement instrument, including its psychometric qualities, is described clearly. - The population of interest and the sampling procedure are defined clearly. - The data collection procedure is clearly described. - The setting in which the study took place is described. - The data analysis procedures are stated in precise terms. - The data analysis procedures are appropriate. Results: the results are presented clearly, the authors provide accurate research results, and there is sufficient evidence for each result, Specific data accompany the result statement, and Tables and figures are used efficiently. Conclusion: in general: Good and the research provides sample data for the authors to make their conclusion. Finally, this was an attractive article. In its current state, it adds much new insightful information to the field. Therefore, I accept that paper to be published in your journal.

Response: Thank you very much for your positive comments about our work. The English usage in our draft was polished by AJE, a reputable language polishing company, and the related proof has been provided with the uploaded files. We sincerely hope that the revised manuscript will meet the publication requirements (Grade A). Thank you!

Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.

Language Quality: **Grade B (Minor language polishing)**

Scientific Quality: Grade B (Very good)

Response: The English usage in our draft was polished by AJE, a reputable language polishing company, and the related proof has been provided with the uploaded files. We sincerely hope that the revised manuscript will meet the publication requirements (Grade A). Thank you!

Company editor-in-chief:

I have reviewed the Peer-Review Report and the full text of the manuscript, 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. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-

review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

Response: Thank you very much for the helpful suggestions. We have added a discussion of the latest information on the role of immune cells in liver ischemia-reperfusion injury in the Discussion section by using the RCA database. It is a very useful writing tool, and we also mentioned it in the Acknowledgments section.

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

Response: We have modified the figure legends in the suggested format and explained the terms and results in more detail. We hope that these changes help present our data in a clearer manner. We sincerely hope the revised manuscript will meet your requirements. Thank you!

Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. 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) 2023.

Response: All images have been displayed in the PPT according to your requirements and uploaded. Thank you!