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PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 85161

Title: Interferon-γ priming enhances the therapeutic effects of menstrual blood-derived stromal cells in a mouse liver ischemia-reperfusion model

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03372482
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Academic Research, Assistant Professor, Associate Professor
Reviewer's Country/Territory: Egypt
Author's Country/Territory: China

Manuscript submission date: 2023-04-20

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-04-22 09:15

Reviewer performed review: 2023-04-22 09:16

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
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) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

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

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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

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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.

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Peer-review model: Single blind

Reviewer's code: 05536533
Position: Peer Reviewer
Academic degree: MS, PhD
Professional title: Academic Research, Assistant Professor, Research Associate
Reviewer's Country/Territory: India
Author's Country/Territory: China

Manuscript submission date: 2023-04-20

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-05-20 14:40

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Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Well conducted study with menstrual blood stem cells

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Peer-review model: Single blind

Reviewer's code: 03948659
Position: Peer Reviewer
Academic degree: PhD
Professional title: Senior Lecturer, Senior Scientist
Reviewer's Country/Territory: Bangladesh
Author's Country/Territory: China

Manuscript submission date: 2023-04-20

Reviewer chosen by: Geng-Long Liu

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Reviewer performed review: 2023-05-25 10:46

Review time: 1 Day and 5 Hours

Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[Y] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
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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

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.