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PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 75421

Title: Soluble factors secreted by human Wharton's Jelly Mesenchymal Stromal/ Stem Cells exhibit therapeutic radioprotection - a mechanistic study with integrating network biology

Provenance and peer review: Invited 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: India

Manuscript submission date: 2022-01-28

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-28 08:04

Reviewer performed review: 2022-01-28 08:40

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Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
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) [Y] Minor revision [ ] Major revision [ ] Rejection

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

SPECIFIC COMMENTS TO AUTHORS

Stem cells isolated from Wharton's Jelly of the umbilical cord are a unique source of MSCs which has been reported to be safe when administered to recipients without inducing any adverse effects or teratoma formation. Recently, we reported that hWJ-MSCs and their conditioned medium have significant therapeutic radioprotective potential in lethally irradiated mice. These findings motivated us to identify a unique feature of hWJ-MSCs over other sources of stem cells for the understanding of its radioprotective mechanism and deciphering the role of the G-CSF present in hWJ-MSCs-CM. Research methods: Propidium iodide staining, endogenous spleen colony-forming assay, and survival study were carried out for radioprotection studies. Homeostasis driven proliferation assay was performed for in vivo lymphocytes proliferation. Neutralization of G-CSF with anti-G-CSF was done to investigate the role of G-CSF in therapeutic radioprotection. Analysis of RNAseq data was performed to find the unique genes of WJ-MSCs by comparing them with bone marrow mesenchymal stem cells, embryonic stem cells, and human fibroblasts. Gene enrichment analysis and protein-protein interaction network were used for pathway analysis. Research results: Co-culture of irradiated murine splenic lymphocytes with WJ-MSCs offered significant radioprotection to lymphocytes. WJ-MSCs transplantation increases the homeostasis-driven proliferation of the lymphocytes. Neutralization of WJ-MSCs-conditioned medium (WJ-MSCsCM) with G-CSF antibody abolished therapeutic radioprotection. Transcriptome analysis showed that WJ-MSCs share several common genes with BM-MSCs and ESCs and also express a high level of unique genes

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such as IL1-α, IL1-β, IL-6, CXCL3, CXCL5, CXCL8, CXCL2, CCL2, FLT-1, and IL-33. It was also observed that WJ-MSCs preferentially modulated several cellular pathways and processes which are responsible for the repair and regeneration of damaged tissues compared to other sources of stem cells. Cytokines-based network analysis showed that most of the radiosensitive tissues have a more complex network for the elevated cytokines. Research conclusions: This study showed the role of cytokine G-CSF present WJ-MSCs-CM in therapeutic radioprotection. Systemic infusion of WJ-MSCs-CM may have significant potential for treating accidentally radiation exposed victims. Research perspectives: WJ-MSCs-CM holds significant therapeutic radioprotective ability and has translational potential for its use during radiation accidents. In General: it's a good paper and the subject of the manuscript is applicable and useful. Title: the title properly explain the purpose and objective of the article Abstract: abstract contains an appropriate summary for the article, language used in the abstract is easy to read and understand, 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. Results: the results are presented clearly, the authors provide accurate research results, there is sufficient evidence for each result. Conclusion: in general: Good and the research provides sample data for the authors to make their conclusion. Grammar: Need Some revision. (Check The Paper Comments). Please provide the following information in the Paper 1. Conflict of Interest 2. Source of Funding Finally, this was an appealing 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: 03738702
Position: Editorial Board
Academic degree: MSc, PhD
Professional title: Senior Researcher, Senior Scientist
Reviewer's Country/Territory: Italy
Author's Country/Territory: India

Manuscript submission date: 2022-01-28

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-28 09:49

Reviewer performed review: 2022-01-28 11:49

Review time: 2 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] 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
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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

I read with great interest this manuscript by Dr. Maurya and colleagues investigating the potential radioprotective effects of hWJ-MSCs and CM by identifying selected soluble factors responsible for the observed effects. The study highlighted the value of G-CSF in mediating therapeutic properties. This work adds new knowledge that can advance the potential use of MSCs as a cell therapy to prevent acute radiation syndromes. The title is informative and the topic is interesting and well presented. The methods are well reported and conclusions are consistent with results. The study is well written and worth publishing after minor revision. My suggestions are below described in a point-by-point list: 1. In the title the authors define mesenchymal cells as "mesenchymal stem cells" but, over the years, scientists have debated the name of these cells, and the term "mesenchymal stem cells" has often been changed to "mesenchymal stromal cells". The authors should change the term “stem” with either “stromal” or at least “stromal/stem” in the title and along the text. 2. On page 6, please extend the acronym HSC in “HSC-niche” 3. On page 7 (material and methods section), in the paragraph “Isolation and characterization of WJ-MSCs”, a briefly description of WJ-MSCs isolation and phenotypic characterization should be added (a new figure 1 showing MSC images and distinctive markers should be added). 4. To prepare the conditioned medium, did the authors try various conditioning times (48 and 72 hours) to verify better efficacy? 5. In Figure 8, to make the individual gene names for clusters 1, 2 and 3 more readable, the resolution should be improved.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05935626
Position: Peer Reviewer
Academic degree: MD
Professional title: Doctor
Reviewer's Country/Territory: Indonesia
Author's Country/Territory: India

Manuscript submission date: 2022-01-28

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-29 16:50

Reviewer performed review: 2022-01-29 20:20

Review time: 3 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] 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
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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

I would like to congratulate the authors for this manuscript. This study is interesting and can bring new perspective. I have some comments about the manuscript: Materials and methods: Please refer related previous study on the methods that you use. Please provide your reasoning for determining the radiation dose of 6Gy and 8.5Gy. Please provide your reasoning for using 200 microliters of conditioned medium in the survival study. If the doses are found from your previous study, please clarify. How many mice were involved in your study? Please provide details about the animals used. About the infusion procedure, please provide details about the procedure and duration for better understanding. Please specify the statistical methods used. Discussion: Please provide the limitations of your study within the methodology. References: Please follow the format for references guidelines. Figures: Please ensure clear and sharp figures for better viewing, in particular figure 6, 7, 8 and supplement figures.