

PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 76458

Title: Role of hypoxia preconditioning in therapeutic potential of mesenchymal stem-cell-derived extracellular vesicles

Provenance and peer review: Invited Manuscript; Externally peer reviewed

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: Spain

Manuscript submission date: 2022-03-17

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-03-20 08:44

Reviewer performed review: 2022-03-20 17:55

Review time: 9 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Dr. Pulido-Escribano et al. addressed a review entitled - "Role of hypoxia preconditioning in therapeutic potential of mesenchymal stem cell-derived extracellular vesicles" - with the aim of showing that hypoxia preconditioning of MSC is a promising strategy to enhance MSC regenerative properties in order to implement cell-free therapy using MSC-derived EV. MSCs support tissue regeneration in both physiologic and pathologic conditions, and it is widely debated whether MSCs contribute directly to renewal/repair of tissue (MSCs differentiate and replace individual components of tissue and/or MSCs secrete extracellular matrix components) or MSCs contribute indirectly by providing a source of key paracrine factors (secretome) that orchestrate tissue repair/regeneration. Indeed, the tissue regeneration effects of MSCs are mediated, at least in part, by paracrine mechanisms that lead to regulation of fibrosis, immunomodulation, stimulation of angiogenesis and stimulation of resident cells to coordinate both tissue regeneration and function recovery. The topic is interesting and well-presented and the title is informative. Minor concern: The authors titled the paragraph 3 as: "CELL THERAPY VS. CELL-FREE THERAPY". However, in this section mainly a description of EV was made. Based on the title, the authors should described the therapeutic applications of both cells and their products, list the strengths and weaknesses of each therapy and, finally, compare them. Otherwise the authors should change the title.

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Title: Role of hypoxia preconditioning in therapeutic potential of mesenchymal stem-cell-derived extracellular vesicles

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05402718

Position: Peer Reviewer

Academic degree: PhD

Professional title: Assistant Professor, Research Associate

Reviewer's Country/Territory: China

Author's Country/Territory: Spain

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Reviewer accepted review: 2022-03-18 00:29

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Review time: 10 Days and 7 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
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Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

In the present study, Pulido-Escribano et al. summarized role of hypoxia preconditioning in therapeutic potential of mesenchymal stem cell-derived extracellular vesicles. Although it is interesting, there are some comments for the authors. 1. Language needs to be improved. For example, "Among the conditions used to induce a better therapeutic response of MSC is the culture of cells in low O₂ concentrations (hypoxia)" is wrong expression. 2. In the page 5, MSC have been isolated from different tissues, such as fatty one, placenta, umbilical cord, synovium, periodontal ligament and bone marrow. What is fatty one? Additionally, the sources of menstruation (PMID, 31864423) and Wharton's jelly (PMID, 32557631) can be added. 3. In the page 6, Exosomes are vesicles generating after fusion of multivesicular bodies with plasma membranes, ranging between 40 to 100 nm, I suggest authors provide some references. 4. The part "CELL THERAPY VS. CELL-FREE THERAPY" is not clear. 5. In the page 8, When oxygen concentrations decrease to less than 5% in tissues, cells have to adapt their metabolism and functions to such hypoxic conditions. Less than 5% is the hypoxic condition, is there any criterion. 4.9% or 0.1% are same one for the hypoxic condition? Please make some detail explanation. 6. Figure 2 should be improved. The basic description for the elements is lacked. 7. Table 3. EV used in medicine therapies derived from hypoxic MSC. I suggest authors added more references. 8. The challenge of MSC-EVs in regenerative medicine should be added.