

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 55168

Title: Mesenchymal stem cell-derived exosomes: Toward cell-free therapeutic strategies in regenerative medicine

Reviewer's code: 03472014

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Senior Lecturer

Reviewer's Country/Territory: Malaysia

Author's Country/Territory: China

Manuscript submission date: 2020-03-15

Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-03-16 05:02

Reviewer performed review: 2020-03-18 11:33

Review time: 2 Days and 6 Hours

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] Grade E: Do not publish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



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SPECIFIC COMMENTS TO AUTHORS

Authors have provided a scholarly written work capturing potential of mesenchymal stem cell-derived exosomes as a cell-free therapeutic strategy in accelerating regeneration. A review on their application for various degenerative diseases is very commendable and the highlight on the contribution of this manuscript. The article provides an essential reference for researchers in this field.

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 55168

Title: Mesenchymal stem cell-derived exosomes: Toward cell-free therapeutic strategies in regenerative medicine

Reviewer's code: 00505755

Position: Editorial Board

Academic degree: PhD

Professional title: Senior Research Fellow

Reviewer's Country/Territory: Japan

Author's Country/Territory: China

Manuscript submission date: 2020-03-15

Reviewer chosen by: Jin-Zhou Tang (Quit in 2020)

Reviewer accepted review: 2020-03-23 00:32

Reviewer performed review: 2020-03-23 06:15

Review time: 5 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 checked="" type="checkbox"/> Grade A: Priority publishing <input 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 checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input 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

This is an interesting study about mesenchymal stem cell-derived exosomes. The MSC-derived exosomes may have great potential for regenerative medicine. The differences of exosomes among differentiation stages of MSCs may be added for the section 4 MSC-derived exosomes.

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 55168

Title: Mesenchymal stem cell-derived exosomes: Toward cell-free therapeutic strategies in regenerative medicine

Reviewer's code: 00504800

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: United States

Author's Country/Territory: China

Manuscript submission date: 2020-03-15

Reviewer chosen by: Jin-Zhou Tang (Quit in 2020)

Reviewer accepted review: 2020-03-21 17:27

Reviewer performed review: 2020-03-27 20:37

Review time: 6 Days and 3 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" 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 type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input 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

The manuscript by Ma et al. provides a fairly comprehensive review of the potential of MSC-derived exosomes for regenerative therapies. The authors briefly review the history of MSC and MSC-derived exosomes, including their biogenesis, characteristics, techniques of isolation, properties, and potential advantages over their parental MSC. The authors then provide a relatively comprehensive review of the animal data on exosomes to treat various diseases. My main critique of the manuscript is that it is very heavily focused on in vitro and animal models and essentially fails to mention any human clinical trials which have either completed accrual or are in progress. A brief literature search revealed two recent (2019) papers reviewing exosomes for clinical use, which cover similar material as the current manuscript, but also review a number of current clinical trials utilizing exosomes (Yin K et al., Biomarker Research 2019; Mendt M et al., Bone Marrow Transplant 2019). The Yin paper in particular is similar in format to the current manuscript. A brief search of ClinicalTrials.gov shows 83 registered interventional therapeutic studies (not including basic science, biobanking and biomarker studies) using exosomes. The authors need to both incorporate the findings from published clinical trials, and summarize disease processes being investigated in active clinical trials for their manuscript to provide benefit to the scientific community over what has already been published. Second, the writing of much of the manuscript related to therapeutic potential of exosomes is not terribly exciting for the reader. Much of the second half of the manuscript is “these authors showed this; those authors showed that”. I think that many of the in vitro and animal study data could be shortened, which would leave room for the authors to mention any clinical trials which pertain to the disease process. Minor comments: Section 2.1: Reference 25 refers to the International Society for Cellular Therapy position paper. To my knowledge,

neurogenic differentiation was not a required characteristic to define MSC in this paper. Figure 1: Please define M1 and M2 cells (macrophages) at first use of the abbreviation. Section 2.2.2: First sentence should be revised to refer to “lodging” of MSC in non-specific tissues. What is meant by “homing to natural ‘walls’”? Table 2: There are some contradicting statements in the table that need to be corrected, such as Membrane filtration: keeps exosomes intact is an advantage, but deformation is a disadvantage – which is correct? “High yield” is listed as both an advantage and a disadvantage for Precipitation. Section 4: First line, should maybe say “ease of isolation” instead of “non-invasive isolation”. Line 4, differentiation of MSCs MAY induce ossification – ossification is a rare event and certainly does not happen in all cases. Section 4.2.1: Can the authors give an example or a reference for exosome production on a large scale using specialized cell lines? Section 4.2.2: Do the authors intend to say that MSC are not stable at -80C, or that exosomes are more stable at -80C than MSC (which should be kept frozen in LN2 or vapor phase)? Section 5.2.1: Top line p. 19, please define HuES9.E1 as a human embryonic-derived MSC line. Section 5.3.2, third paragraph middle of p. 23, please revise the sentence containing “acting as a ceRNA to sponge miR-138-5p can regulate Sirt1” – this is unclear.