

PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 82656

Title: Immunomodulation: the next target of mesenchymal stem cell-derived exosomes in the context of ischemic stroke

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06317368

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Surgeon

Reviewer's Country/Territory: China

Author's Country/Territory: China

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Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-12-28 01:31

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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 Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
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

SPECIFIC COMMENTS TO AUTHORS

The article is focused on the MSC-Exos and related immunomodulatory functions in ischemic stroke. The authors review studies about immune responses after IS, detailed mechanisms of MSC-Exos, as well as prospect of clinical applications of MSC-Exos. The article is well-organized and conclude cut-edge results. Please pay attention to following comments. 1. In the Abstract, Line 8, the authors should notice that exosomes could not represent all important features of MSCs, for example, cell differentiation and paracrine function. 2. In the Abstract, Line 14, please pay attention to the grammar, especially the plural form of nouns and following verbs. 3. In the Abstract, Line 16, the word "stimulating" would be replaced by "promoting". 4. In the Abstract, Line 18, "immune inflammation" is not a common phrase, "inflammation" alone is enough. 5.

In the 1st paragraph of Introduction, Line 5-7, the "4.5-hour time window" is based on studies of thrombolysis. Many studies about thrombectomy have already surpassed this restriction. Ref.: DOI: 10.1056/NEJMoa2207576 . 6. In the 1st paragraph of Introduction, Line 10, like the previous comment, due to the expansion of treatment window of intraarterial thrombectomy, nowadays most patients who did not receive

either thrombolysis or thrombectomy is because very severe or very mild clinical manifestation, or large core infarction based on radiologic results. 7. In the 1st paragraph of Introduction, Line 13-14, there is lack of citation(s). 8. In the 1st paragraph of Introduction, Line 20-24, do IS patients be commonly prescribed with antibiotics? 9.

In the 1st paragraph of Introduction, Line 24-25, "By 2050, more than 500 million people per year will experience a stroke " is not a precise description. 10. In the 3rd paragraph of Introduction, Line 2-3, it is not wrong to emphasize immunosuppression in the prognosis of IS, but whether it is the primary cause is not sure yet. If the author found any article hold the opinion then it should be cited. 11. In the Section "IMMUNE RESPONSE AFTER IS", it would be better if the author would re-organize this section. Since the section talks the immune responses mainly by cell types, a sequence like "myeloid cells" "lymphoid cells" "granulocytes" might make it easier for read and understand. 12. In the 2nd paragraph of the Section "IMMUNE RESPONSE AFTER IS", Line 29-31, the author should give the specific biomarkers that microglia recognize on ischemic neurons and cite relevant article. 13. In the 3rd paragraph of the Section "IMMUNE RESPONSE AFTER IS", Line 1-2, there is lack of citation about the sentence "Neutrophils are the initial blood-derived immune cells to cross the BBB and invade ischemic tissues, and they can be detected as soon as 1h after the event." 14. In the 1st paragraph about Microglia of the Section "MSC-Exos regulate the immune response through cells", for contents in this section, I would recommend to talk more about details of some important studies. 15. In the 1st paragraph about Astrocytes of the Section "MSC-Exos regulate the immune response through cells", about the sentence "It has been demonstrated that MSC-Exos reduces A1-Ast expression and improves inflammation. They act primarily through the Nrf2-NF-κB signaling pathway in the regulation of Ast activation", whether these results came from studies of ischemic stroke or other brain diseases? Detailed methods of these articles should be added. 16. In the



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1st paragraph about Astrocytes of the Section “MSC-Exos regulate the immune response through cells”, the sentence “Moreover, a recent study identified high LCN2 expression in a mouse transient middle cerebral artery occlusion (tMCAO) model and detected that IS patients with higher plasma LCN2 levels were more likely to develop a post-stroke infection” is confusing, did they do both human and animal studies? 17. In the 2nd paragraph about Astrocytes of the Section “MSC-Exos regulate the immune response through cells”, what does the word “mast” mean in the sentence “Recently, the in vitro studies reported that MSCs improved brain function after transplantation mainly by reducing the number of mast Ast and GFAP overexpression through inhibition of p38 MAPK, JNK, and its downstream targets p53 and STAT1 activation by paracrine factors”? 18. About the sub-title “FROM BENCH TO BEDSIDE: LIMITATIONS OF EXOSOMES THERAPY IS AND THE COUNTERMEASURES”, please re-check the grammar of the sentence. 19. In Figure 2, the word “Mucclle” should be “Muscle”.

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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
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	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The current review is very well written with good illustrations and tables. The authors are only advised to check one of the heading, "EXOSOMES AS A REPLACEMENT THERAPY FOR MESENCHYMAL STEM CELLS ON STROKE", is this in context of stroke or ischemic stroke as the other headings given by authors are in the context of ischemic stroke.