



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 65857

**Title:** Modulating poststroke inflammatory mechanisms: Novel aspects of mesenchymal stem cells, extracellular vesicles and microglia

**Reviewer's code:** 02446223

**Position:** Editorial Board

**Academic degree:** PhD

**Professional title:** Postdoctoral Fellow, Professor

**Reviewer's Country/Territory:** Italy

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2021-03-16

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-03-17 09:12

**Reviewer performed review:** 2021-03-22 09:12

**Review time:** 4 Days and 23 Hours

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 Grade E: Do not publish            |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



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#### **SPECIFIC COMMENTS TO AUTHORS**

The review is very exhaustive and precise. It clearly describes all the "partners" of the question. The title reflects the main subject and figures and tables help to follow the description.



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 65857

**Title:** Modulating poststroke inflammatory mechanisms: Novel aspects of mesenchymal stem cells, extracellular vesicles and microglia

**Reviewer's code:** 03372146

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2021-03-16

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-03-17 00:58

**Reviewer performed review:** 2021-03-26 02:32

**Review time:** 9 Days and 1 Hour

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



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#### **SPECIFIC COMMENTS TO AUTHORS**

The manuscript by Xin et al first described the different roles of two different phenotypes of microglia in the treatment of ischemic stroke, suggesting that changing the activation status of microglia might be an interesting stroke treatment approach. In recent years, MSCs and EVs have been reported to affect post-stroke inflammatory response, but the exact mechanism of this treatment is still unclear. In this review, the authors summarize the interaction between MSCs and MSCS-EVs with activated microglia, and elaborate on the inflammatory targeting mechanism by which MSC-EVs exert therapeutic effects. The logic of this paper is clear and the structure is rigorous, but one of the deficiency is that the therapeutic effect of MSCs and MSC-EVs is mainly described in this paper by promoting the M2 polarization of microglia, which leads to the change of various signaling pathways. However, it is not appropriate to place MSC, MSC-EVS and microglia in the same position in the title of this paper, so it is suggested to be modified. Besides, this article illustrates the mechanism of MSC-EVs regulating microglia activity involving cytokines, neurotrophic factors, transcription factors and microRNAs. However, the microRNA mentioned in this article is not reflected in the figure. It is suggested to add this part in the figure.



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 65857

**Title:** Modulating poststroke inflammatory mechanisms: Novel aspects of mesenchymal stem cells, extracellular vesicles and microglia

**Reviewer's code:** 03757295

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2021-03-16

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2021-03-24 12:44

**Reviewer performed review:** 2021-03-27 01:53

**Review time:** 2 Days and 13 Hours

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



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#### **SPECIFIC COMMENTS TO AUTHORS**

The authors reviewed recent articles investigating the roles and mechanism of MSC and MSC-EVs on microglial activity after ischemic stroke, especially the M1 M2 dynamics. The article is well structured. First, the authors discuss the pathophysiology of ischemic stroke and the role of microglia, then discuss the therapeutic role and the molecular mechanism of MSC and MSC-EV treatment. - The entire article focused on the mechanism of how the MSC and MSC-EV affect microglia. Figure 2 should include important signaling pathways/mechanisms on microglial polarization mentioned in the article. An alternative solution is to merge figure 1 and figure 2 together and summarize the molecular impacts of MSC and MSC-EV on microglial. - Line196-Line 204 Regarding BBB disruption, I suggest adding some recent studies about the mechanism: TNFa (Chen et al. Cell Death & Disease, 487 (2019)) microglial phagocytosis (Haruwaka et al., Nature Communications, 5816 (2019)) - Some format and grammar issues: Citation should come before the punctuations, e.g. "[42]," instead of ",[42]". Typos like: "[98, 124].." Line385 - 390 multiple tenses were used in one paragraph. Please recheck the format and grammar. I recommend accepting this article after minor revision.



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 65857

**Title:** Modulating poststroke inflammatory mechanisms: Novel aspects of mesenchymal stem cells, extracellular vesicles and microglia

**Reviewer's code:** 03811784

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Professor

**Reviewer's Country/Territory:** Iran

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2021-03-16

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2021-03-24 17:28

**Reviewer performed review:** 2021-03-31 03:32

**Review time:** 6 Days and 10 Hours

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



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## **SPECIFIC COMMENTS TO AUTHORS**

The Manuscript by Monzur et al. reviews the “novel aspects on mesenchymal stem cells, extracellular vesicles and microglia on poststroke mechanisms”. Information collected in the manuscript entitled “Modulating poststroke inflammatory mechanisms—novel aspects on mesenchymal stem cells, extracellular vesicles and microglia” are in a logical sequence with appropriate analysis with figures and table to that contain data to inform the readers. The manuscript builds upon previous important research that is appropriately referenced. The data from this manuscript does move the canon of knowledge forward and may be considered by the Top 10-20 % of the research field. The manuscript is novel and interesting to warrant publication in “World Journal of Stem Cells” after minor revision. 1) The Abstract section are too long. It should be concise and comprehensive. 2) Please mention the novelty of this review in the “introduction section”. 3) The characterization of mesenchymal stem cells must be mentioned in more detail. For this reason, you can use and refer the following paper which explain it elaborately and completely: Isolation, culturing, characterization and aging of adipose tissue-derived mesenchymal stem cells: a brief overview. *Brazilian Archives of Biology and Technology*. 2016; 59. 4) Also, telomere length shortening is related to neurodegenerative disease, stroke inflammatory and aging. It could be better discuss about the telomere shortening as clinical perspective in the text of the manuscript. You can use and refer the following papers: Telomere shortening as a hallmark of stem cell senescence. *Stem cell investigation*. 2019;6. Telomere length: a potential biomarker for the risk and prognosis of stroke. *Frontiers in neurology*. 2019 Jun 13;10:624.



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 65857

**Title:** Modulating poststroke inflammatory mechanisms: Novel aspects of mesenchymal stem cells, extracellular vesicles and microglia

**Reviewer's code:** 06040039

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** Italy

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2021-03-16

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2021-03-25 08:08

**Reviewer performed review:** 2021-04-12 03:01

**Review time:** 17 Days and 18 Hours

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



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#### **SPECIFIC COMMENTS TO AUTHORS**

I really appreciate your contact in resolving the review of this paper, titled Modulating poststroke inflammatory mechanisms—novel aspects on mesenchymal stem cells, extracellular vesicles and microglia. The review of manuscript NO 65857, I have already finished the preview of the current manuscript. More comments information, you will find information below: 1. "When activated after stroke, microglial cell activation includes four distinct phenotypes such as ramified, intermediate[p1] , amoeboid, and round phenotypes [26]. The ramified microglia refer to the resting state, whereas intermediate state microglia have larger cell bodies and shorter bumps. The amoeboid microglial cell body, on the contrary, is larger and displays shorter bumps or even no bumps at all, similar to round microglia that are found in the lesion center [26]. Based on these morphological characteristics and their secretion patterns, microglia are characterized as M1 type or M2 type." It should be combined with the expression of specific markers of M1 or M2 here for a better macrophage characterization. 2. I have a word document, download attached file in word please.