

### **Responses for the Reviewer's #1 comments and suggestions:**

#### **Comments:**

I would like to congratulate the author for this manuscript. The review is interesting and brings current perspective. I have some comments about the manuscript: Figures (1 and 2): please add some explanations or statements that describe the figures for better understanding and readability (both figure 1 and 2). References: Please do the referencing according to the guide for authors. Some references are old, please replace with the current ones. Accordingly, related published articles in the World Journal of Stem Cells may be considered. There are some 'ahead of print' references from previous years publications, these references should already be published normally, not in 'ahead of print' status, please correct this.

#### **Response:**

Dear Reviewer,

The author wishes to thank this Reviewer for the valuable comments regarding this review manuscript. All your suggestions have been taken into account:

1. The figures have been improved and additional callouts have been added.
2. References have been improved: "ahead of print" removed, newer publications added

### **Responses for the Reviewer's #2 comments and suggestions:**

#### **Comments:**

In the present review, the Author summarizes main results obtained in vitro, in preclinical, and in clinical studies regarding beneficial effects of MSCs in cases of ischemic diseases. Overall, the topic is interesting in the field of regenerative medicine and a large number of experimental findings are described. However, the manuscript needs a further language revision to improve the style of writing and to amend grammar errors/typos. For example: Repetitions at pag. 11: "the concept of ..... (Brychtova et al, 2019)" Repetitions at pag. 12: "Moreover, the exosomes protected ..... protecting myocardial cells from apoptosis ..." Pag.7. "cells cardiac". (cardiac cells?) Pag.7. "markers CMCs". (CMC markers?) Pag.7. "Although in vitro MSCs show potential for differentiation towards CMCs, for differentiation of native MSCs into

building cells damaged organ tissue in vivo has a significant impact on many other factors, including their ability to colonize the damaged area of the organ as also the viability of these cells after administration [59]" (explain better!) Pag.8: "MSCs, thanks to their ability to secrete a series of soluble molecules, including interleukins and anti-inflammatory cytokines, which can modulate the immune response [79,80]." (delete: which?) Pag.10: ... has been shown to facilitate (attenuate?) myocarditis by ... Further observations Fig.1. Albeit briefly, Figure 1 should be described in the legend. Pag.12: ... by Musialek et al. (reference number is missing) Finally, results obtained in recent works deserve to be included: Pag. 8. About MSC neural differentiation Neural differentiation of human adipose-derived mesenchymal stem cells induced by glial cell conditioned media. PMID: 29737535. Autophagy Promoted Neural Differentiation of Human Placenta-derived Mesenchymal Stem Cells. In Vivo. PMID: 34410948. Pag. 8. About MSC immunomodulatory properties Effects of High Glucose Concentration on Pericyte-Like Differentiated Human Adipose-Derived Mesenchymal Stem Cells PMID: 33925714.

### **Response:**

Dear Reviewer,

First of all, the author wishes to thank this Reviewer for the valuable comments regarding this review manuscript. Based on these comments the author decided to submit the manuscript to a professional proofreading company to improve the quality of the language. The figures have been improved and additional callouts have been added. Missing references have been add. The author also decided to add references suggested by the reviewer.

### **Responses for the Reviewer's #3 comments and suggestions:**

#### **Comments:**

Diseases caused by ischemia are one of the leading causes of death in the world. Current therapies for treating acute myocardial infarction, ischemic stroke, and critical limb ischemia do not complete recovery. Mesenchymal stem cells, whose immunomodulatory abilities and paracrine activity can ease inflammation and promote regeneration of damaged tissues, seem to be a hope and alternative therapy. This review aims to summarize the current knowledge on the mechanisms of action of

MSCs and their therapeutic effects in the treatment of ischemic diseases. In General: it's a good paper and the subject of the manuscript is applicable and useful. Title: the title properly explains the purpose and objective of the article Abstract: abstract contains an appropriate summary for the article, the language used in the abstract is easy to read and understand, and 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, and 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 and edit the following information in the Paper 1. Conflict of Interest. 2. Source of Funding. 3. Writing references according to the terms of the journal 4. The result and discussion must be in one paragraph. Finally, this was an attractive article. In its current state, it adds much new insightful information to the field.

**Response:**

Dear Reviewer,

The author of this manuscript would like to express gratitude for the review. Based on these comments the author decided to submit the manuscript to a professional proofreading company to improve the quality of the language. Missing information has been added as per the authors guide

**JOURNAL EDITOR-IN-CHIEF'S REVIEW REPORT**

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

**Manuscript NO:** 80788

**Title:** Mesenchymal stem cells in ischemic tissue regeneration

**Journal Editor-in-Chief (Associate Editor):** Shengwen Calvin Li

**Country/Territory:** United States

**Editorial Director:** Jia-Ru Fan

**Date accepted review:** 2022-12-12 20:15

**Date reviewed:** 2022-12-12 20:16

**Review time:** 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good		<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Major revision

## **JOURNAL EDITOR-IN-CHIEF (ASSOCIATE EDITOR) COMMENTS TO AUTHORS**

EIC Specific comments: 1) Fig 1 and Fig 2, MSC: Mesenchymal stem cell concept should be explicitly defined: What types of MSC origins? A table should be provided to specify the origins of MSCs and their specific therapeutics linked to clinical trials of specific organs [<https://clinicaltrials.gov/>], as not all MSCs with the same capacity as illustrated in the Figures. Otherwise, it might mislead the readers. 2) Figure 2. Exosomes or secretome: Their perspective definitions? Differential effects? M1? M2? All of these should be provided and referenced with current literature citations. As all three reviewers demanded detailed descriptions of the figure legend: the author should not ignore the requests. 3) "In 1970, Friedenstein et al. [19] discovered an exceptional type of cell that has been extensively researched over the years for its potential use in regenerative medicine to treat ischemic damage[20]. These cells, called mesenchymal SCs (MSCs), reside in both young and adult donors [e.g., umbilical cord, amniotic fluid, umbilical cord blood (UCB), placenta, adipose tissue (AT), bone marrow (BM), dental pulp, and others], which has been a particular and exciting source of SCs for many years, mainly for autotransplantation and allotransplantation." These MSCs of different origins came with differential potentials, reflecting on the heterogeneity, which should be emphasized in the literature review with ample

citations. Thus, the standardized protocols defined by The International Society for Cellular Therapy should be stated upfront. 4) Inappropriate citations: "These methods emphasize improving the quality of and extending the patient's life, but they cannot fully reverse the effects of tissue ischemia [7-11]." Five articles jammed but did not reflect on which specific. Neither did this lead nor give clues to the reader about specificity. 5) Abbreviations should be provided by spelling out the term first appearing. E.g., "One of the primary and best-known sources of MSCs is BM[38,39]. Cells with similar morphology and biological characteristics can also be found in other tissues collected from adult donors, such as peripheral blood, AT, dental pulp, and fetal tissues such as UCB and cord Wharton jelly (WJ)[40]." Citation 40 did not support the sentence references without specific chapters, specifically for the heterogeneity, reflecting on their discrepancy of efficacy. 6) The detrimental effects of MSCs have not been fully discussed, such as MSCs-related cancer progression and resistance to therapies. 7) The abstract is too generic to attract the readers: Some specific insight should be framed to allure specific attention to hint the readers to follow up with this particular manuscript. Why are you the author?

Dear Editor,

First of all, the author wish to thank Editor for the valuable input regarding this review manuscript. Based on these comments the author decided to extend the manuscript by adding two tables:

- Tabele 1) Minimal criteria recommended by International Society for Cellular Therapy for defining mesenchymal stem cells
- Tabele 2) Selected clinical trials of mesenchymal stem cell-based therapy in ischemic diseases.

Moreover, the detailed descriptions of the figure legend has been added. Inappropriate citation [40] has been changed. Corrections have also been made to the use of abbreviations. The abstract has been extended with additional information contained in the manuscript.

Regarding point 6, I would like to comment that negative effects have been in individual cases, but in general MSC therapies are considered as safe.

Sincerely,

Renata Szydlak