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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 64790

Title: Effects of living and metabolically inactive mesenchymal stromal cells and their derivatives on monocytes and macrophages

Reviewer's code: 05868353
Position: Peer Reviewer
Academic degree: PhD
Professional title: Director
Reviewer's Country/Territory: China
Author's Country/Territory: Brazil

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Reviewer performed review: 2021-03-11 13:14
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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Please see file "Reviewer Comment" attached.

Overall Comment:

The review article by Sant'Ana AN et al. entitled "Effects of living and metabolically inactive MSCs and their derivatives on monocytes and macrophages" reviewed recent laboratory and clinical findings on either living or metabolically inactive MSC's effects on monocytes and macrophages. This review came out at the right time as more attentions were paid to the therapeutic potentials of metabolically inactive MSCs. Besides, clinical trials involving the use of MSCs as therapeutic agent are being actively conducted internationally despite the mechanism of actions (MoA) underlining MSC's therapeutic effects in multiple indications remained illusive. The authors discussed recent findings regarding the MoAs underlining MSC's therapeutic effects, which should be of interest to a board range of readers working in the MSC field.

Immunomodulation capabilities of MSCs play critical roles in ameriolating inflammation and promoting tissue repair. Such functions of MSCs are being heavily discussed in this review. The authors frequently used terms like "immunomodulatory", "immunoregulatory" and "immunosuppressive" in different parts of the article sometimes in an interchangeable manner. This could be a little bit confusing to readers new to the field. MSCs by themselves are indeed immunomodulatory but not only immunosuppressive. For example, MSCs may facilitate the release of IL-10 directly/indirectly to limit the proliferation of CD4+ and/or CD8+ T-cells and inhibit antigen-specific T-cell responses. These actions could be considered immunosuppressive. On the other hand, IL-10 mediated M2 polarization of macrophage and activation of Treg cells are anti-inflammatory but not entirely immunosuppressive. Moreover, MSCs promoted clearance of bacteria by macrophage, which should not be considered

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immunosuppressive (discussed by the authors in this review as well from line 274~281). Taking together, immunosuppression (particularly on T-cells) is only part of MSC's immunomodulatory function. The author may have to carefully review the use of terms so readers new to the field could have a clear idea regarding MSC's capabilities and functions. Replacing "immunosuppressive" with "anti-inflammatory" in some statements could be a choice.

The authors may also consider include more discussion regarding clinical application of MSCs.

Specific Comment:

Line 48: The authors may consider switching the term "immunosuppressive" to "immunoregulatory" or "immunomodulation".

Line 49: Regarding "living" and "metabolically inactive" MSC, it seems that the authors are trying to define two (2) sub-categories of cells (According to Figure 1, "living" and "metabolically inactive" MSCs are regarded as 2 sub-categories of cells). In such a case, the authors may consider state it clearly that "metabolically inactive" MSCs are actually dead cells (by "heat inactivation" or other means) so readers will have a clearer idea.

Line 74: Change "neuron cells" into "neural cells" or "neurons" depending on the authors intention.

Line 134: Better provide examples of pro-inflammatory cytokines.

Line 135: Better provide examples regarding how M2 macrophages modulated inflammation and promoted regeneration.

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Line 175: May be immunoregulatory or immunomodulating will be better than immunosuppressive? Subsequent discussions (e.g. line 177~179 and line 187~188) also mentioned "modulation of macrophage's and monocyte's ..... by living and metabolically inactive MSCs".

Line 240~247: The authors should provide reference materials. The authors may also consider stating clearly the biological functions of MRC1, CD163, CD226, etc.

Line 282~295: May be 1 or 2 more reference papers for this paragraph?

Line 373~374: The authors may consider elaborate more on the topic "After phagocytosis, monocytes migrate to other body sites carrying the regulatory properties of MSCs.".

Line 506: Instead of "for some disease models", better state the diseases/indications may benefit from MSC-based treatments.

Line 521~524: References are needed for these claims/descriptions (go through lung capillaries, emboli formation).

Line 549~553: The authors may consider explain in details why an enhanced macrophage phagocytosis resulted in improvement of lung injury.