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Dear Dr. Editor

The authors would like to thank you very much for the valuable comments and for the opportunity to improve our paper and to response the comments from you and reviewers. The comments and suggestions were examined point-to-point and the answers have been provided below. We have increased our paper considering the reviewers suggestions and the changes in the manuscript were highlighted using bold text. We now hope that our paper is sufficiently adequate for publication in World Journal of Stem Cells.

Responses to Editor issues raised:

(1): The grant document was uploaded

(2): The original figure was uploaded separately as Power-Point editable format

(3): Our figure is original, elaborated for this submission

Sincerely,

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Response to Reviewer

The authors would like to thank you for the careful analysis of our paper. We have increased our paper considering your suggestions and the changes in the manuscript were highlighted using bold text.

Overall comments:

Thank you for your observation about the use of "immunomodulatory", "immunoregulatory" and "immunosuppressive" terms. Sorry for the confusing in the text. The authors reviewed the manuscript and changed the terms deemed to be inappropriately used.

Regarding clinical applications, we agree with your suggestion, but we not found literature data to increase our discussion. The attention of entire description in our article is related to the mechanisms of action describing monocytes and macrophages cooperation and this description is not easily found in clinical manuscripts. This difficulty is described on the follow paragraph:

"In clinical trials, performing some cellular analysis is difficult and may not be possible. Moreover, clinical improvements are the main evaluated outcomes. We will briefly introduce some reports that showed descriptions of clinical improvement using MSCs with a possible involvement of monocytes and macrophages."

Specific Comment:

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

Thanks for your comment. Sorry for our inadequate mention. We have changed the term "immunossupressive" to "immuneregulatory".

 # 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.

Thanks for your suggestion. The authors agree with your observation and have increased this sentence to clarify our idea.

"Here, we review the effects of living ***(metabolically active MSCs)*** *and metabolically inactive MSCs* ***(dead cells that lost metabolic activity by induced inactivation)*** *and their derivatives (****extracellular vesicles, soluble factors, extract and microparticles)*** *on the profile of macrophages and monocytes and the implications for immunoregulatory and reparative processes."*

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

We have followed your suggestion and have changed the term "neuron cells" to "neural" cells.

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

The authors have considered your comment and have increased the text.

"M1 macrophages are characterized by a cytotoxic phenotype and by the production of reactive species and pro-inflammatory mediators ***such as IL-1, IL-6, IL-12, IL-23 and TNF-α*** [30,27]***."***

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

Thanks for your suggestion. We have included an additional phrase in this paragraph.

"Meanwhile, M2 macrophages presents a healing profile, pronounced by anti-inflammatory and angiogenic molecules production, as TGF-β, IL-10, VEGF and EGF, that support reparative processes [30,27]***."***

 # 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".

Thanks for your observation. Sorry for our inadequate mention. We have changed the highlighted term.

"Their results have demonstrated that these substitutes maintain ***the immunomodulating*** *properties that induce a regulatory phenotype in monocytes and macrophages."*

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

Thanks for your comments. We have provided the reference in the first phrase and have improved the text, considering the biological functions.

"MRC1 encodes CD206, which along with CD163 and CD163L1, belong to the scavenger receptors family, that mediate the remodeling function after tissue damage [42]***. CD93 is important to phagocytosis and clearance of apoptotic cells, while CD226 is involved in monocyte migration. Further, LILRB1 is an immunoglobulin-like receptor involved in MHC-I mediated immunosuppression."***

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

The authors have considered your commentary, but we not have found other papers describing this same topic.

 # 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."

Thank you. We have followed your suggestion and increased this topic.

"In addition to their paracrine action, MSCs are phagocytized by monocytic cells in an active process. After ***in vitro*** *phagocytosis, monocytes* ***acquire phenotypic and functional changes of CD14++CD116+ immune regulatory intermediate monocytes, such as upregulated expression of PD-L1 and CD90 surface molecules and IL-1b, IL-6, IL-8, IL-10, and TGF-β cytokines, whilst expression of the pro-inflammatory TNF-α decreases*** [33]***. In vivo, monocytes which phagocytized MSCs assume the same anti-inflammatory profile and*** *migrate to other body sites****, mainly to the liver,*** *carrying the regulatory properties of MSCs* [33]*.* ***Further,*** *macrophages* ***also phagocyte MSCs and*** *acquire an* ***anti-inflammatory M2*** *phenotype,* ***characterized by increased IL-10 and TGF-β expression*** [34]*."*

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

We have followed your suggestion and cited the model disease for this presented effect.

"Together, these data suggest that, ***at least in some sepsis models,*** *monocytes that had phagocytized inactivated MSCs acquired their immunoregulatory properties and reduced inflammation* [39, 81]*."*

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

Sorry for our fault, we have included the reference.

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

The authors have considered your comments and have increased the description.

"The enhanced of host macrophage phagocytosis could promote a clearance of invading microorganism, that associated with suppressive pro-inflammatory cytokine secretion, may improve clinical outcomes, since lung injury is associated with high inflammatory response and bacterial burden."