



PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

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Title: Senescent mesenchymal stem/stromal cells and restoring their cellular functions

Reviewer's code: 01552211

Position: Peer Reviewer

Academic degree: MD

Professional title: Research Assistant Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

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Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-05-27 09:55

Reviewer performed review: 2020-05-30 10:03

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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 Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input 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 checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" 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



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General comments Among the novel treatment strategies available, mesenchymal stem/stromal cells (MSCs) have garnered huge attention by both researchers and clinicians owing to their regenerative and immunomodulatory properties that make them particularly suitable for therapeutic application in immune-mediated conditions. Of course, this implies a number of manufacturing issues that should be solved to accelerate the adoption of MSCs as a bedside reality. One issue regards the process of senescence that MSCs undergo upon a number of passages in-culture, that hamper their biological properties. In this scenario, the present review is of relevance for translational medicine since it shows the state of the art of improving/expanding the potential therapeutic effects of MSCs. The work is driven by appropriate methodology, the data are clearly presented, and the bibliography is appropriate and updated. However, there are a few of issues that need to be addressed. Here below, please, find more detailed comments. Specific points a) First, I would pose a semantic question: should we still use the term 'transplantation' when referring to MSC therapeutic use? In my opinion, this word leads to a misinterpretation of this kind of therapy. Indeed, despite the use of stem cells, the effect is completely different from that intended for bone marrow transplantation (correct use). The difference lies in the fact that bone marrow transplantation is a once-in-a-life treatment and results in the reconstitution of the hematological compartments, including the immune system. By contrast, MSC administration represents a novel immunotherapy and not a kind of transplantation since they do not stably engraft in patients, but aid the target organ to overcome the injury while modulating the peripheral immune response. Therefore, I suggest to replace the term "MSC transplants" with "MSC administration". b) The title should be changed as follows: "Senescent mesenchymal stem/stromal cells and restoring their cellular functions". c) Please introduce a reference where the criteria for MSC definition are stated (Dominici M., et al. *Cytotherapy* 2006). d) Please, introduce a



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comment on the possible genetic instability of senescent MSC. e) Why the short paragraph at the end of page 7 is highlighted in yellow? f) In each section, the authors are jumping from human and mice results that jeopardize the message. Please, re-organize the paragraphs accordingly. g) A note of caution on the possible clinical translation of the evidence presented should be added since they are collected mostly in in vitro studies. h) Please replace the word 'impirod' with 'impaired' on page 13. i)

Please explain the acronyms when used the first time. Avoid abbreviations when the term is used less than three times. j) Please insert page numbers at the bottom of the pages.