

This is an excellent and extensive review of a highly significant topic. There is no question that MSCs will be a focus of multiple therapeutic approaches far into the future. Just a couple of minor points-

We are very pleased that this reviewer considers manuscript an "excellent and extensive review". We agree with the reviewer that MSCs' secretome currently is the focus of research in many groups working on Regenerative Medicine and we would modestly hope that our work could somehow serve as a reference in this field.

We have addressed the reviewers' comments and modified the text accordingly. Changes are highlighted in red in the manuscript.

1) In the section entitled "Role of EVs in Cell-to-cell communication", there is reference to "Toll-Like" receptors, but toll is misspelled (tool).

We thank the reviewer for pointing out this spelling mistake that has now been corrected.

2) In the first paragraph of the Discussion, it is stated "...approval as a drug is proving tough...", while this is true, a more professional way of saying this would be "... is proving to be elusive..."

Indeed the change suggested by the reviewer is more in accordance with a formal text. We thank the reviewer for this suggestion.

3) While the literature review is extensive with an excellent choice of references, there is another paper that could be considered because it fits perfectly into the sense of this paper, supports the conclusions that the secretome is key and includes an additional cytokine released by MSCs that did not receive much (if any) consideration in this review: Salazar, K. D., S. M. Lankford, and A. R. Brody. Mesenchymal stem cells produce Wnt isoforms and TGF β 1 that mediate proliferation and pro-collagen expression by lung fibroblasts. *Am J Physiol, Lung Cell Mol Physiol*, 297: 1002-1011, 2009.

After revising this point we have realized that, in the first version of the manuscript, we failed to highlight other important effect of the MSCs' secretome, which is the mitogenic activity of some of the secreted factors, something highly relevant for the regenerative potential. We have now introduced a short section specifically dedicated to this point (page 10, text in red) where we have cited the paper indicated by the reviewer and other papers that have published relevant results in the this particular subject.