

Response to reviewers

We appreciate the reviewers for their helpful comments. We have revised the manuscript, resulting in significant improvement over the previously submitted manuscript.

Comments from Reviewer 1

The paper by Kim and Kim is an interesting review on the use of Mesenchymal stem-like cells to produce Extracellular Vesicles, with the aim of a cell-free therapy. The paper is interesting and well written, Title, Abstract and Keywords well reflect the main subject of the manuscript and the Background is adequately described. The authors described pros and cons of this approach in well-organized paragraphs. The references are appropriately cited, with clear and exhaustive figures and tables. My only suggestion is to also emphasize the putative problems related both to the origin of PSC, and to the factors used to produce Mesenchymal-like cells and to derive EVs.

Response: We appreciate the comments. To further discuss the potential problems that can be raised during iMSC derivation and producing EVs, we have added description on this issue at the last paragraph of page 8.

Comments from Reviewer 2

In this review, the authors highlight the importance in therapeutic field of extracellular vesicle (EV) compared with native MSC or MSC derived from ESC or iPSC. The topic is interesting and no similar review are present in literature. There are some criticisms:

1) The title of the review does not seem appropriate to the content. Please modify

Response: We have changed the title as “Generation of mesenchymal stem-like cells for producing extracellular vesicles”, since this article also include protocols for deriving MSCs from somatic cells.

2) The paragraph “CONTENTS OF MSCs AND iMSCs” should be revised as sometimes there is confusion between information for MSC from ESC and MSC from iPSC.

Response: We appreciate the reviewer's comment. To obviate the misleading, we have moved the discussion on the distinct contents in EVs and their parental cells to under the subheading of ‘The distinct contents of iMSC-EVs and their future application’. Also, the title of this section has been changed to ‘comparison of MSCs and iMSCs’, and we found that the remaining contents are now more

focused on the biological traits between MSCs and iMSCs.

3) In the paragraph "CONTENTS OF MSCs AND iMSCs" the author state that often EVs from pluripotent cell-derived have a distinguishable profile with respect to those from MSCs. Why? Suggest an explanation for this.

Response: We apologize for being misleading. We removed this sentence - we realized that this sentence is not necessary, because our thought was to discuss the biological difference between EVs and their parental MSCs, as now shown in page 13 and references no. 63, 64, and 65.

Furthermore, the authors state that hES-MSCs have more primitive characteristics than hMSCs. But is this an advantage in terms of content of EV?

Response: It is quite difficult to answer this now, but we think it is very important issue that should be pointed out. We have newly added an implicative sentence describing its usage for therapeutic purpose; 'It would be important to explore whether hES-MSCs' primitiveness affects the therapeutic potential of their secretome, including EVs.'