

Reviewer #1: Thank you for the opportunity to review the manuscript by Fafian-Labora et al. On the whole the manuscript is somewhat unstructured and rambling. The manuscript requires restructuring & clear delineation of animal and human studies. Figure 1 adds little or nothing to the paper and should be removed. A table summarising the review's finding would be beneficial, should the revised manuscript be re-submitted or submitted elsewhere. On a more positive note this review is wide-ranging in its content and well referenced throughout: a notable omission is the work by Brohlin et al. (PLoS One. 2012;7(9):e45052. doi: 10.1371/journal.pone.0045052. Epub 2012 Sep 17) on human MSC-induced neurite outgrowth. All references are appropriate and present in both the text and reference list.

Answer #1:

Thank you for your positive comments. The manuscript has been restructured for better comprehension. The figure 1 has been divided in different parts along the text in this new version of the manuscript to better comprehension. The manuscript is focusing in the new knowledge in the field of mesenchymal stem cells' senescence along the last three years, this is the reason of the omission of article by Brohlin *et al.*

Reviewer #2: This manuscript entitled "Effect of Aging on Behaviour Mesenchymal Stem Cells Effect of Aging on Behaviour Mesenchymal Stem Cells" is a review paper to discuss the aging behavior of mesenchymal stem cells (MSCs). Authors make an in-depth discussion of MSC aging including cell senescence, autophagy, mitochondrial stress and exosomal activity. This review paper is interesting and would attract the readers in the stem cell field.

Answer #2:

Thank you for your positive comments.

Reviewer #3: This review is excellent, compactly summarizing a large volume of valuable information regarding the mechanism of senescence as well as possible rejuvenation of MSCs. I believe this review will contribute to promoting the development of MSC- or MSC-EV-mediated regenerative medicine. Minor concerns: 1) In page 13, line 21 the word "nhibition" should be corrected as "inhibition". 2) In page 13, line 24 the word "containeing" should be corrected as "containing".

Answer #3:

Thank you for your positive comments.

1. The word has been corrected in this new version of the manuscript.
2. The word has been corrected in this new version of the manuscript.

Reviewer #4: Thank you for your great manuscript about aging on behavior of mesenchymal stem cells. It's very interesting and very valuable to readers.

Answer #3:

Thank you for your positive comments.

Reviewer #5: In this manuscript, the authors reviewed the biological features in the literature on MSC senescence over the last three years. The content of this manuscript is systematic and comprehensive. It can reflect the main progress of this research direction. The thesis is well written with clear hierarchy, clear logic and prominent emphasis. It could provide some references to the readers. However, there're still some issues which should be addressed. 1. Telomerase and cell senescence are closely related. So, the author should discuss this topic and add the relevant content. 2. The authors should compare young and old stem cells to identify the major differences (shape, function, characteristic expression of molecules, etc.) So, major revision should be recommended for this manuscript.

Answer #5:

Thank you for your positive comments.

1. We explained in the introduction this review is focusing in autophagy, mitochondrial stress and exosomal activity. However, telomerase and cell senescence are closely related, we consider that telomerase deserve a new review only for itself.
2. We considered that a major explanation about young and old stem cells could drive confusion because of the different cellular mechanisms existing in the cell could induce senescence as in young as in old stem cells by differences in the culture medium.

Reviewer #6: 1. The title is not consistent with the content of the manuscript as the context focused mainly

on the mechanisms that induce stem cells cellular senescence, please modify the title? 2. Where is the core tip? 3. Minor English language editing is required as there are certain typos and errors as the sentence "has also been also linked to mitochondrial fission and fusion events" in the introduction section. 4. Figure legends should be positioned at the bottom not at the top of the images.

Answer #6:

1. We consider that the title is consistent because this manuscript is focusing in the process through mesenchymal stem cells are suffering or transforming themselves and their behaviour because of aging, which can be natural (in vivo) or induced (in vitro).
2. The core tip is is the new version of the manuscript.
3. The sentence has been corrected in this new version of the manuscript.
4. Figure legends have been positioned at the bottom of the images in this new version of the manuscript.

Reviewer #7: The manuscript "Effect of Aging on Behaviour of Mesenchymal Stem Cells", is a useful presentation of factors that influence the aging of MSC cells, important in the application of MSC based regenerative therapies. The manuscript shows that the age of MSC harvested from young tissues like umbilical cord differ to those isolated from adult bone marrow, and presents a series of markers that can differentiate MSC age. There are presented also a series of treatments with compounds such as vitamin C, curcumin or quercetin that can reverse this senescence. Subsequently, the authors present a series of mechanisms that induce cellular senescence. However, two of the subtitles, namely "Mesenchymal stem cells and mitochondrial stress" and "Mesenchymal stem cells and autophagy" are not very clearly presented. A systematization of the factors that influence these processes would be useful. On the other hand the last part "Mesenchymal stem cell-derived extracellular vesicles" is very nice and clear presented. Additional comments: 1. Unclear phrase: "MSCs are easily isolated and amenable to culture expansion in vitro because of the natural desire to test MSCs in many diverse clinical indications, which are exemplified by the rapidly expanding literature base that includes many in vivo animal models." 2. Minor spelling mistakes: "Non-coding like miR-1292" should be "non-coding RNA like miR-1292", the RNA is missing; "nhibition" (page 13); "containeing" (page 13).

Answer #5:

Thank you for your possitive comments.

The subtitles have been changes in this new version.

1. The phrase has been changed in this new version of the manuscript.
2. The words have been corrected in this new version of the manuscript.