

September 26, 2014

Dear Editor,

Please find the edited manuscript in Word format (file name 13499-review).

**Title:** Molecular Mechanism of Extrinsic Factors Affecting Anti-Aging of Stem Cells

**Author:** Tzyy Yue Wong, Mairim Alexandra Solis, and Ying-Hui Chen, and Lynn LH Huang.

**Name of Journal:** *World Journal of Stem Cells*

**ESPS Manuscript NO:** 13499

The manuscript has been improved according to the suggestions of reviewers:

1. First reviewer's comment:

This article overall reviewed the extrinsic factors in micro-environment affecting the anti-aging role of stem cells, including the hypoxic environment, genome stability, mitochondria integrity, epigenetic regulators, calorie restrictions, nutrients and vitamin D. It is innovative and helpful for understanding the molecular mechanisms of anti-aging effects of stem cells. The article is also well written. Revisions:

1) The authors did not cite the two figures in the text, please add them;

Corrections:

Figure 1B is cited in Line7 of "Definition of extrinsic factors that alter stem cells properties".

Figure 1A and 1B are cited together in Line26 of "Definition of extrinsic factors that alter stem cells properties".

Figure 2 is cited in Line23 of "Hypoxia induced by micro-environment".

Figure 2 is cited again in the final Line of "Mitochondrial property changes upon stem cells aging".

2) In figure 2, there are some promising cross-talks among different pathways of the intracellular factors. It is suggested to complement 1-2 paragraphs to summarize the correlated research.

Corrections/reply:

For this part, we have made a few citations of the Figure 2 in the text (as mentioned above). We apologize that there were no citations in the beginning, and that may have

caused some inconveniences during the reading of the manuscript. In other words, the pathways in Figure 2 are actually described throughout the manuscript, starting from the “Mechanisms of stem cell anti-aging”. Thank you very much for your valuable comments.

## 2. Second reviewer's comments:

The reading of the paper suggests the following comments:

1. In the paragraph “Hypoxia induced by micro-environment” the expression of marker of aging p16 should be better explained. Furthermore, the authors should cite a recent paper about the interplay between HIF-1 $\alpha$  and p53 in hypoxia condition (Kilic Eren M, Tabor V. The role of hypoxia inducible factor-1 alpha in bypassing oncogene-induced senescence. PLoS One. 2014 Jul 1;9(7):e101064).

### Corrections:

Sorry for the use of some over-expressive terms, we have rephrased the sentence as this:

“Under condition of 1% O<sub>2</sub>, HIF-1 $\alpha$  activation led to decreased extracellular signal regulated kinase (ERK), followed by decreased p16 expression <sup>[37]</sup>. The decreased expression of the aging marker p16 helped MSC escaped cellular aging *in vitro* <sup>[37]</sup>.”

Thank you for your suggestion, we have included it:

“A recent study further confirmed that 1% O<sub>2</sub> down-regulated DNA damage responsive molecules, including ATM/ATR, Chk1, and Chk2, and also cellular aging markers, including senescence-associated- $\beta$ -galactosidase, H3K9me3, heterochromatin protein 1- $\gamma$  (HP1 $\gamma$ ), p53, p21, and p16 <sup>[38]</sup>.”

2. At line 11 of paragraph “Genome stability linked to stress induced by micro-environment”, the sentence “Under stress of Sirt1 ablation.... DNA damage” should be corrected as follow: “Under condition of stress, Sirt1 ablation promotes HSPCs expansion, leading to increased DNA damage”.

### Corrections:

“Under condition of stress, Sirt1 ablation increased Hoxa-9 expression and DNA damage in HPSCs.”

3. The Figure 1 and 2 should be cited through the text.

minor revision is required for the submitted review paper.

### Corrections:

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properties”.

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Figure 2 is cited in Line23 of “Hypoxia induced by micro-environment”.

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