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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 67533

Title: Impact of senescence on the trans-differentiation process of human hepatic progenitor-like cells

SPECIFIC COMMENTS TO AUTHORS

The manuscript entitled "Impact of senescence on the trans-differentiation process of human hepatic progenitor-like cells" reported by Bellanti F et al. investigated the effects of senescence on the trans-differentiation capacity and mitochondrial metabolism of the human HepaRG cells. Overall, the manuscript is well-constructed and it provide valuable information to the readers. Following are some suggestions for the authors. 1. For the study of liver metabolism and hepatic progenitors using trans-differentiated HepaRG cell line, the functions of hepatocyte-like cells are important. In Figure 3, besides of gene expression, albumin secretion capacity, activities of CYP3A4 and γ -glutamyl transpeptidase should be investigated. Or at least, the protein level of these candidates should be presented by Western-blotting or immunofluorescence staining. 2. How are the expressions of markers of both progenitor and differentiated cells (such as CD49a, CD49f, CD184, EpCAM and CK19) in P10 and P20 HepaRG cells before 2-week DMSO exposure? The changes of the expression of these markers will represent the trans-differentiation process. 3. In page 9, line 281. "Figure 2A" is supposed to be "Figure 4A".

REPLY

We thank the reviewer for his positive comments, and for his suggestions. We



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considered his recommendations and further experiments were performed.

1. Functional analysis of albumin secretion, CYP3A4 and γ -glutamyl transpeptidase activity was performed, and results are shown in Figure 5. Accordingly, the abstract (page 2, lines 29-31; page 3, lines 1, 8-10), methods (page 7, lines 1-15), results (page 10, lines 11-19), discussion (page 12, line 4), and figures (page 26) were modified in the new version of the manuscript.
2. According to the point raised by the reviewer, we performed analysis of HepaRG trans-differentiation markers before and after DMSO treatment by flow cytometry, and the results are shown in Figure 3. Changes were made in the methods (page 6, lines 1, 15-17) and figures (page 24) of the new manuscript.
3. The mistake was corrected.