Format for ANSWERING REVIEWERS

May 21, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16943).
Title: Common stemness regulators of embryonic and cancer stem cells

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Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 16943

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

In the revised version we included:

1. Additional phrase in the end of Introduction p2.
2. New Discussion section p29
3. Additional paragraph on Jak/Stat signaling p6
4. Additional Tables I (ESC biomarkers) and II (CSC biomarkers.
5. Additional Figure 1A and B (Signaling pathways ESC and CSC)

2 Revision has been made according to the suggestions of the reviewer
(1) **00007461**:
QUE: For example, a Table summarizing the known stem cell markers for each tumor type with reference. The authors should include a description of the rationale and approaches that led to the identification of these markers that mark CSCs, with a discussion of the pros and cons.
ANS: New **Table II** (Cancer Stem cell biomarkers),
New paragraph in Discussion (2nd paragraph, p29), describing pros and cons about biomarkers

QUE: a diagram outlining each signaling pathway discussed should be included.
ANS: . Diagram showing signaling pathways **New Fig.1A and B.**

QUE: On pg 21, 3rd paragraph from the top of page,"Targeting the stemness-like properties of CSCs with epigenetic modifiesrs...., the authors are asked to make a clear statement of the problem . As presented is confusing. Specifically: as discussed, use of DNMT inhibitors are used to treat cancer.... on the other hand they state:" their low methylation state of CSCs may indicate...."What is the point they wish to make with these conflicting statements?
ANS: Corrected paragraph "Investigating the methylation signature of CSCs permits identification of modifiers that can target their stemness properties, leading to increased tumor sensitivity to chemotherapy. Current DNMT inhibitors used in cancer therapy, such as Decitabine (5'-aza-2'deoxycitidine) act through incorporation into DNA therefore causing adverse side effects [341]. Less hazardous alternatives include use of small molecule inhibitors such as SGI-1027 [342] and dietary phytochemicals[342] on p21

QUE: Lastly, grammatical and spelling errors should be corrected.
ANS: Grammatical and spelling errors were corrected.

(2) 01236209:
QUE: The authors also claimed to discuss the potential use of ESCs and CSCs to design next generation biological and pharmaceutical approaches for regenerative medicine and cancer therapies. However, this part is too weak, and needs an in-depth discussion.
ANS:. New Discussion, last 2 paragraphs on p31.

Minor comments: (1) Pay attention to the gene names. For example, mouse gene should be "Myc", and human gene should be "MYC".
Corrected
(2) There are many typos and misspelling in the text, such as "c-muc" in the introduction section.
Corrected

(3) For the biomarkers, the authors only introduced surface markers for ESCs. Therefore, it is unnecessary to mention the intracellular markers (nestin, SOX2, Musashi-1 and Bmi-1) in CSCs.
ANS: In ESC intracellular factors (Oct4, Sox2, Nanog) are also considered biomarkers however they were presented in detail as transcription factors thus we omitted a detailed description in the biomarkers section but include them in the new Table I (ESC biomarkers). The expression of these factors in CSC is correlating with their stemness potential therefore we included them in the new Table II (CSC biomarkers).

(4) Page 18, "It is well-known that Myc is involved in the regulation of 15% of genes in the human genome 275 and regulates pro-tumorigenic transcription factors including KRAS, AKT, PTEN and p53 276, 277." Indeed, PTEN and p53 are tumor suppressors, but not pro-tumorigenic factors. Moreover, KRAS, AKT, and PTEN are signaling molecules, but not transcription factors.
ANS: Corrected in 1st paragraph p18:" It is well-known that Myc is involved in the regulation of 15% of genes in the human genome [275] and regulates important pro-tumorigenic factors including KRAS and AKT, and tumor-suppressors PTEN and p53 [276, 277]"

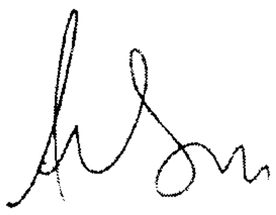
(3) 02439754
QUE 1. Provide some insights about the epigenetic reprogramming in CSC.
ANS: This is discussed in p31 2nd paragraph (Discussion).

QUE 2. Some typo's in the text. For examples, p.1 Introduction, line 8: A typo: "c-muc" should be "c-Myc"? p. 6, 2nd paragraph, typo: "CC13" should be "CD13"? 3. p.3, section: CSC biomarkers in solid tumors: What is ESA? Embryonic surface antigen? Please provide the full name when it is first present in the text
ANS: All typo's and other errors were corrected.

(4) 02446014:
QUE: I would include a second table summarizing the various markers discussed in the section "General properties and markers for embryonic/pluripotent and cancer stem cells
ANS: Table I ES cell biomarkers, Table II Cancer Stem Cell biomarkers

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Stem Cells*.
Sincerely yours,



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