

06 03 2019

To Editors-in-Chief,
World Journal of Stem Cells
Tong Cao, DDS, PhD, Doctor, Professor,

Shengwen Calvin Li, PhD, Adjunct Professor, Research Scientist,
Senior Research Fellow

Carlo Ventura, MD, PhD, Director, Full Professor

Answer to Reviewers:

1. Reviewer

Answer: We apologize and believe that there was a misunderstanding on our part in the described "that the Portuguese data were accounted". The first reviewer's comments that "one of the criteria of selection of article was to be written in English" is true; because we did not use any Portuguese database, we used only the English words for this systematic review in the search of the PUBMED, EMBASE, OVID and COCHRANE LIBRARY databases that were all in English. We will correct the text, page 6: Only studies reported in Portuguese and English were evaluated, altered by "Only studies reported in English were evaluated".

On the inclusion of "in vitro" in the title and abstract. **Answer:** We have complied with the two suggestions and they have been included in the title and abstract.

The reviewer commented that "although hBSC can express nanog, Oct4 and Sox2 and other pluripotency markers, there is a lack of strong evidence that these cells are truly pluripotent." **Answer:** We believe there is controversy on this subject in the literature. Our group also has demonstration of the

expression of these three markers, as well trilineage differentiation from those cells: hBSC. The results were *in Press*.

“In fact, the existence of pluripotent ASCs that do not form teratomas was previously described in BM, considering that these cells have unique patterns of DNA methylation in some genes and it is suggested that the non-formation of teratomas would be associated with these epigenetic characteristics^[40].”

Other comments by the reviewer "In some sections, the author also mentioned that hBSC do not form teratomas, but in others they do," "Clarifie in the text."

Answer: We believe it is not necessary because there is a paragraph, on page 22, which we discussed, see below.

“In fact, the existence of pluripotent ASCs that do not form teratomas was previously described in BM, considering that these cells have unique patterns of DNA methylation in some genes and it is suggested that the non-formation of teratomas would be associated with these epigenetic characteristics^[40].”

About the Figure 4. **Answer:** This figure was registered and the cytochemical were done by the first author Camila Maria Ribeiro Pacheco in her Master thesis. This is from hBSC and the number is 1.324.098 (11/16/2015) of Human Ethical Committee of Pequeno Príncipe Faculty. It was not published in any journal. We included this information in the legend of the figure 4.

2. Reviewer.

1. The title should explain that this systematic review is organized for *in vitro* studies. **Answer:** We attend this suggestion and included the term “*in vitro*” as well we modified the title for new Title: **IN VITRO DIFFERENTIATION CAPACITY OF HUMAN BREASTMILK STEM CELLS: A SYSTEMATIC REVIEW.**
2. Why the author didn't use the term differentiation in the search strategy as a systematic review intended to detect the number of the *in vitro* studies

performed to hBSCS differentiation into three lineages? **Answer:** We could explain this to the aim of concentrating efforts for research on the cell origin: human breastmilk and cellular type: stem cells.

3. I think there is a conflict as the authors reported that they included articles in English Language only and in order they reported that they selected articles in Portuguese and English Languages. **Answer:** We apologize and we believe that there was a misunderstanding of our part. We have used only the English words for this systematic review in searching on PUBMED, EMBASE, OVID and COCHRANE LIBRARY databases that were all in English Language. We will do correction on the text, page 6: Only studies reported in Portuguese and English were evaluated, changed for "Only studies reported in English were evaluated".
4. The discussion section is too long and I think that they should focus on the studies they were selected according to their included criteria. **Answer:** **Answer:** We agree with you, but we believe that we have made this approach to emphasize the discussion, being a review article on the subject of scarce literature.

3. Reviewer

1. The order of appearance of the reference is very confusing. The introducing ends with citation 10 and then in the next Chapter (materials and methods) continue with 51. Then in the Discussion references begin again from number 11. The references should be numbered consequentially as they are cited for the first time in the text, this is not to apply the manuscript correct. **Answer:** We apologize, our confusions with references of the table and text as well the last consideration was due for intention to attend PRISMA. We have reviewed all references in the text and done all needed corrections. See reviewed manuscript.
2. The Figure 4 is original or is for another paper? Please Clarify. **Answer:** This figure is original. It was registered and the

histochemical was made by the first author Camila Maria Ribeiro Pacheco in her Master thesis. This is from hBSC and the number is 1.324.098 (11/16/2015) of Human Ethical Committee of Pequeno Príncipe Faculty. It was not published in any journal. We included this information in the legend of the figure.

3. In table 2-There is an error in the description of marker O4 and GFAP, please correct both. We have done both correction.

Finally the 20190406 Comments:

It is an interesting systematic review about cellular differentiation capacity of human breastmilk cells, however the following should be considered:

1. The title should explain that this systematic review is organized for *in-vitro* studies. **Answer:** We attend this suggestion and included the term "*in vitro*" as well we modified the title for new Title: **IN VITRO DIFFERENTIATION CAPACITY OF HUMAN BREASTMILK STEM CELLS: A SYSTEMATIC REVIEW.**
2. Why the authors didn't use the term differentiation in the search strategy as the systematic review intended to detect the number of the *in-vitro* studies performed for hBSCs differentiation into three lineages. **Answer:** We could explain this to the aim of concentrating efforts for research on the cell origin: human breastmilk and cellular type: stem cells.
3. I think there is a conflict as the authors reported that they included articles in English language only and in other places they reported that they selected articles in Portuguese and English languages. **Answer:** We apologize and we believe that there was a misunderstanding of our part. We have used only the English words for this systematic review in searching on PUBMED, EMBASE, OVID and COCHRANE LIBRARY databases that were all in English Language. We will do correction on the text, page 6: Only studies reported in Portuguese and English were evaluated, changed for "Only studies reported in English were evaluated".

4. Where is the table of RoB for the selected studies? **Answer:** We have not made this table.
5. The discussion section is too long and I think they should focus on the studies they were selected according to their inclusion criteria. **Answer:** We agree with you, but we believe that we have made this approach to emphasize the discussion, being a systematic review on the subject of scarce literature.
6. English editing is preferred. **Answer:** We have attached the English Review Certification Certification by Sworn Translator and Commercial Interpreter by the Commercial Board of Paraná State, with the submission.

I apologize, but we have review the authors name, we have a mistake, the second author is Priscila Elias Ferreira with the same affiliation of the first author, this not Vanessa Mello.



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