

Dear Editor and Peer review experts

The authors are honored to being able to answer the inquiries raised by formatting and content of our manuscript titled “Human **adult pluripotency – facts and questions –“ invited manuscript ((code 02566952)). We are grateful this work ignited your interest and hope it will make an impact challenging the way the still enigmatic question of human adult pluripotency is regarded.**

Answer to the Editor

E1 Please revise the manuscript according to the review report and my comment

Answer – proceeded

E2 Please provide the author contributions. See the format in the attachment file-revision policies. The format of this section should be like this:

Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed research; Wang CL, Zou CC, Hong F and Wu XM performed research; Xue Jz and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed data; and Wang CL, Liang L and Fu JF wrote the paper's. And answer all of the reviewers' comments carefully (point-to-point). -

Answer – proceeded, thank you very much

Abbreviations that appear for the first time need full names. –

Answer -modified this where appropriate, thank you very much

4. Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.

PMID (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>) DOI

(<http://www.crossref.org/SimpleTextQuery/>)

Answer PubMed citation number and DOI citation have been added to all references, wherever applicable. All the authors have been listed for each reference. All the references have been revised and modified according to journal style.

Answer to reviewers

First of all the authors wish to thank the reviewers for the time and effort taken in correcting the manuscript. We appreciate the creative input that consistently improves the quality of this submission.

Reviewer #1

1.The Editorial “Human adult pluripotency-facts and questions” presents time-line advances on stem cell biology knowledge, nicely highlighting the knowns and unknowns. With the exception of recommending briefly mentioning preconditioning of adult stem cells as strategies to increase stem cell endurance in cell-based therapeutics, or perhaps linking recent findings as reported in the following publication: Bashiri H, Amiri F, Hosseini A, Hamidi M, Mohammadi Roushandeh A, Kuwahara Y, Jalili MA, Habibi Roudkenar M. Dual Preconditioning: A Novel Strategy to Withstand Mesenchymal Stem Cells against Harsh Microenvironments. Adv Pharm Bull. 2018

Aug;8(3):465-470. doi: 10.15171/apb.2018.054. with the STAP controversy could further complete the picture of main areas of research in stem cell biology.

Author answer R1. We are grateful for the positive comments and even more grateful for the interesting suggestion. We have added both the comment and the reference inside the text and thank you very much for this remark.

2. Minor typographic recommendations include: - Terms “in vivo” and “in vitro” should be italicized -Abbreviated terms should be fully explained in its first appearance in text, missing for “MPTCs” and “STAP”

Answer R2 corrected this, thank you very much, MPTC was a typo, an abbreviation list was added to avoid cumbersome in-text details

3. -Review format of cites, many with bracketed numbers following authors names and typing mistakes, like Ref [48] -Add et al., after first 6 authors -

Answer R3 the references have been revised and reformatted

There are 2 Fig.2 legends (correct “stess” in Fig 2 legend) -Page 1, line 8 review text in brackets Page 2, line 38 review fragmented sentence, before “Anti-aging” and add a verb to the sentence starting “It worth...” afterwards - Terms “ca as”; { instead of [twice in text; some brackets unneeded and other missing, remove “(4F)”; “isle” for islet -Page 3, line 1, remove “after” -Bold subtitle “Bone...” -Review punctuation throughout the document -Page 5, add the term “differentiated” following “terminally”

Author answer R4. We are grateful for the remarks and sorry this mistakes. Corrected

Reviewer #2

The manuscript from Labusca et al. is an interesting review describing the recent findings about the isolation from mammalian natural tissues, or the production in stressful culture conditions, of pluripotent stem cells from adult, differentiated cell types. The review is very interesting and updated in its collection and description of current knowledge on these very elusive cells with great applicative potential, and the authors describe very well what are the still open questions and challenges for this rising scientific field.

We are grateful for the positive remarks.

I find it worthy of publication after a minor revision: 1. English should be thoroughly checked (I saw several errors) and corrected (for example remember that “phenomena” is the plural word for “phenomenon”).

Author answer R1= corrected, thank you very much, manuscript has been submitted to professional English language check as requested.

2. Page 7-12, References: please check the style of the references, there are often numbers between brackets after an author name, I don’t understand what they mean.

Answer R3= references have been corrected and re formatted as requested

3. Page 13, Table 1: in the legend you mention an asterisk marking the Yamanaka factors, but in the Table no asterisk is present, please correct.

Answer R3=Corrected

4. Page 14: please change “Figure 2” with the appropriate “Figure 1”. Furthermore, in the legend you mention two kinds of interactions: a) undirected (mutual) and b) directed, but in the figure is not possible to understand which interactions are type a) and which are type b), please clarify.

Answer R4= corrected as appropriate, thank you very much

5. Page 15, Figure 2: Please correct the sentence “Normal human dermal fibroblasts (NHDF) cell line after 48 hours intentional absence of CO₂ in the incubator have modified their morphologic characteristic and adopt culture appearance of pluripotent cells A.” with “A) Normal human dermal fibroblasts (NHDF) cell line after 48 hours intentional absence of CO₂ in the incubator have modified their morphologic characteristic and adopt culture appearance of pluripotent cells.”

Answer R5 = done, thank you very much

Reviewer #3

WJSC-42863 In the present review, the authors explained in detail about the human adult stem cell pluripotency, especially focusing on dedifferentiation conditions. The review may provide readers and investigators with good information. However, it is recommended that “ageing (factors)”-related effects should be added. There are many reports on the alterations in proliferative capacity and pluripotency in cells collected from aged people (patients). Please describe full names for several abbreviations in the manuscript, and check the typographical errors.

Answer to reviewer

We are grateful for the positive comments

Indeed ageing related effects on stem cell phenotype and we are grateful for this remark.

Mention about ageing as potential stressful phenomenon has been added in the manuscript.

Abbreviation list has been added and manuscript has been checked for typos and English Language edited