

Hypoxia-preconditioning of human adipose-derived stem cells enhances cellular proliferation and angiogenesis: A systematic review

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Hypoxia-Preconditioning of Human Adipose-Derived Stem Cells Enhances Cellular
Proliferation and Angiogenesis: A Systematic Review
Journal of Clinical and Translational Research

Dear Dr Forte,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Jan 11, 2022.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author.

You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: Thanks for your submission.

This is a comprehensive literature review regarding hypoxia preconditioning on human adipose derived stem cells. Interestingly, the authors found conflict conclusion among included papers regarding the influence of hypoxia preprocessing on cell proliferation, and draw the conclusion support the opinion from majority studies. However, I'd like to see the author provides an explanation of the unique study. What's the possible reason for the different outcome? Is an improvement on that study needed to correct the conclusion?

Reviewer #2: This is an interesting topic and worth discussing. However, there needs to be more research done to make this a complete review. There are a lot of gaps, missing research, and reference to cells other than hADSC. I recommend taking a deeper dive and resubmit. Below are my detailed recommendations and points to consider.

There needs to be language revision for inconsistencies and grammatical and spelling errors.

Why are HUVECs being discussed so often in the review about hADSC? Stick to the hADSC for the majority of the review with HUVECs as additional data. In its current state, the portion about HUVECs is more substantial than the discussion about hADSC.

Is there a legend for Figs. 5 & 6? This would be easier than searching through the legends.

Why would bone marrow-derived MSCs be the next step to investigate? There are other cells types with differing oxygen tensions that may be more interesting to compare.

What was the concentration of oxygen used in the incubators in the articles? Were they the same, or did they differ between studies?

How did the researchers control for changes in oxygen tensions with media changes and passaging when it was not chemically induced or in a closed system?

More figures would be beneficial.

It would be nice if the review went into more detail and depth. As it is now, it is so high level that the value is diminished.

Cite the actual articles, not the reviews.

I searched for articles and came up with 41 that match the criteria to date and 33 that match the criteria through 2020. There are a lot of articles that are left out based on the search criteria. Include more relevant articles.

Authors' response

Reviewer #1: Thanks for your submission.

This is a comprehensive literature review regarding hypoxia preconditioning on human adipose derived stem cells. Interestingly, the authors found conflict conclusion among included papers regarding the influence of hypoxia preprocessing on cell proliferation, and draw the conclusion support the opinion from majority studies. However, I'd like to see the author provides an explanation of the unique study. What's the possible reason for the different outcome? Is an improvement on that study needed to correct the conclusion?

We thank the reviewer for this important comment. At a closer look into Pilgaard et al's publication the author mentions the use of a non-standard medium for culture of these cells, herein being the possible source for this discrepancy between this study and the rest, as culture mediums have been brought up as causing an effect on the properties and characteristics of stem cells. A small paragraph has been added in the discussion section as a with a brief explanation of why these results were reported by pilgaard et al. Thank you.

Reviewer #2: This is an interesting topic and worth discussing. However, there needs to be more research done to make this a complete review. There are a lot of gaps, missing research, and reference to cells other than hADSC. I recommend taking a deeper dive and resubmit. Below are my detailed recommendations and points to consider.

We thank you for your review and comment. Unfortunately cells other than Human adipose derived stem cells are out of the scope of this review, but this will surely make a great topic for another publication. We wanted to focus on the effects of hypoxia preconditioning specifically on proliferation and angiogenesis of HADSC as this is our current area of research

There needs to be language revision for inconsistencies and grammatical and spelling errors.

We thank you for your review and comment. Regarding language and spelling, we have passed our document through Grammarly and sent the document to spell revision by our co-authors and have taken the necessary changes to the manuscript.

Why are HUVECs being discussed so often in the review about hADSC? Stick to the hADSC for the majority of the review with HUVECs as additional data. In its current state, the portion about HUVECs is more substantial than the discussion about hADSC.

Thank you for your comment. As our initial questions and hypothesis touches upon the capability of stem cells to produce angiogenesis, HUVECs and their analysis is currently the best way to determine the angiogenic capability of stem cells, in other words HUVEC's test the angiogenic capability of stem cells. This why we feel we must discuss HUVECs to

determine the change in angiogenesis with hypoxia. Thank you

Is there a legend for Figs. 5 & 6? This would be easier than searching through the legends. Figure legends are attached to their figures within the text, to make it easier we have included an additional page at the end of the document with all Figure legends. Thank you

Why would bone marrow-derived MSCs be the next step to investigate? There are other cells types with differing oxygen tensions that may be more interesting to compare.

We thank you for your comment, this is correct, and we have corrected this statement. As all cell lines need to be studied.

What was the concentration of oxygen used in the incubators in the articles? Were they the same, or did they differ between studies?

Thank you for your question, although they differed per study, as some used 1, 2, or 3 concentrations they were all maintained within the same range. The exact concentration of oxygen and other hypoxia inducing materials can be found in Table 1. Under the hypoxic model tab.

How did the researchers control for changes in oxygen tensions with media changes and passaging when it was not chemically induced or in a closed system?

Thank you for your question. All of the included studies in our review had cells that had hypoxia induced either chemically or within a closed atmospheric system. Thus, ensuring no changes in oxygen tension with passaging or medium changes.

More figures would be beneficial.

We thank you for your comment. We have added an extra figure, as figure2. Thank you

It would be nice if the review went into more detail and depth. As it is now, it is so high level that the value is diminished.

Thank you for your review and comment. Many interesting topics and discussing may be made regarding hypoxia and human adipose derived stem cells, however these may be out of the scope of this article. These are great topics for very interesting separate reviews. Thank you

Cite the actual articles, not the reviews.

Thank you for your comment. New citations have been added additionally to sections were reviews were cited.

I searched for articles and came up with 41 that match the criteria to date and 33 that match the criteria through 2020. There are a lot of articles that are left out based on the search criteria. Include more relevant articles.

Thank you for your valuable review. A secondary search by our two independent investigators was made on January 6, 2022 with a range limit to the date of the original search. Although many articles are in the present literature examining the effect of hypoxia on proliferation and angiogenesis, many of these articles are focused on cells from either Non-Human donors such as rats, mice or rabbits as well as Non-adipose derived stem cell lineages such as bone marrow being the most common lineage. We are confident that our search although not perfect has been comprised the most accurate Human adipose derived stem cells, that their donors are in good health without any comorbidities that may confound the results.

2nd Editorial decision
08-Jan-2022

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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: