Manuscript number: BSR-2020-2038
Manuscript title: Synovial Membrane Mesenchymal Stem Cells Conditioned Medium Increases Chondrogenic and Chondroprotective Markers in Inflammatory Chondrocyte
Recommendation: Major revision invited

Dear Dr Widowati

Thank you for submitting your paper to Bioscience Reports for consideration.

Your paper has now been assessed by two independent reviewers and I am pleased to say that the reviewers found your paper to be suitable for publication in Bioscience Reports; however, they have suggested some major revisions that are required before your paper can be considered for publication.

If you decide to revise your paper as suggested by the reviewers, please resubmit it along with a description of the changes, a response to the reviewers and a tracked version of your revised paper, within 3 months of the date of this letter. It is important to ensure that the revised paper satisfies all of the reviewers' main concerns, otherwise it may be declined outright at the revised stage.

To submit a revised version of your paper, please use the link below, uploading the revised version of the paper, a cover letter, and a document detailing the response to the reviewers indicating how the manuscript has been revised.

https://bioscirep.msubmit.net/cgi-bin/main.plex?el=A1KH5MIO4A6dkj7I1A9ftd6AuIhSRabaDGezsTbtOQgZ

Please note, as the corresponding author, it is your responsibility to relay this decision to the co-authors. If you wish to forward this email, please remove the above link as it will automatically sign into your account when opened.

We look forward to receiving your revised paper, and thank you for choosing Bioscience Reports to publish your work.

Yours sincerely

Ricardo Correa
Associate Editor
Bioscience Reports

Associate Editor Comments:
As indicated by the reviewers, additional experiments are still required.

Reviewer #1 (Comments to the Authors (Required)):

General comments: I have a doubt, all this work was done only with the only sample "from fresh knee joint biopsies of one patients with severe osteoarthritis (Kellgen-Lawrence grade IV)) in Dr ....."?

Minor revisions and absolutely necessaries: 1) I do not have native English, but from what I know, it

deserves an English review, for sure.
2) On the other hand, the methods lose some small details referring to the concentration of antibiotics used, but it should refer to mg / mL or Units / mL.
3) As for the figures, we need more. I also think it is important to have figured in the results with histograms or dot - plot of flow cytometry analysis and the evidence of demonstration of the pluripotency through the photographs of the trilineage differentiation of these particular cellular type: the Synovial Membrane Mesenchymal stem cells.
4) There is a need to improve the image quality; in the abscissa, the graphics are barely visible, poor quality.
5) All figures need their number to the identifier.

Reviewer #2 (Comments to the Authors (Required)):

Firstly, the osteoarthritis cell model was induced by IL-B. OA cells were cultured with appropriate concentrations of SMSCs-CM and IGF-1, and the changes of chondrocyte formation and protective markers before and after OA cell culture were observed. The overall thinking is very clear, but some of the results are slightly weak.
1: the authors believe that SMSCs-CM induced by IGF-1 can enhance the expression of cartilage protection markers in OA cells, and it seems that the induction of IGF-1 is the key, but the title only emphasizes the role of SMSCs-CM. 2: whether the authors should add a group of OA cell models induced by IGF-1 alone as a control can better explain the significance of co-culture of IGF-1 and SMSCs-CM.
3: if conditions permit, the addition of a set of Western-blot experiments in figure3 (markers of metalloproteinases) and figure4 (markers of cartilage hypertrophy) may be more persuasive.

Editorial Office comments:

1. Should your article be recommended for acceptance, high-quality versions of any artwork (including figures and schemes) will be required for production. As poor-quality artwork can result in delays in the publication process, please ensure that artwork has been prepared in accordance with our guidelines and is uploaded during the submission process of your revised paper. For more information, please see our Figure guidelines: https://portlandpress.com/pages/figure_guidelines

2. Please include and clearly indicate a suitable ‘Data Availability Statement’ section within the main text of your manuscript. This section should be placed at the end of the main manuscript text and match that given in our submission system. The Data Availability Statement should include information and access links (where applicable) for any mandated datasets (according to this Data Policy) that are not provided within the paper as a table, figure or supplementary file.

Mandatory deposit is required for the datasets listed below:
-Structural/crystallographic data for both macromolecular structures and small molecules
-Protein and nucleic acid sequence data (this includes RNASeq data)
-Functional genomics and molecular interactions/proteomics/metabolomics data
-Computational models
-Genetics data (genetic polymorphisms; genotype data)

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2) On the other hand, the methods lose some small details referring to the concentration of antibiotics used, but it should refer to mg / mL or Units / mL.

Answer:

1) The manuscript has been edited the english language and grammar (attached the certificate)
2) From 1 donor, we could culture and produce cells with Mesenchymal Stem Cells (MSCs) characteristic (more 95% CD90, CD44, CD73, CD105, negative for CD19, CD34, CD45, HLA-DR). We sub-cultured MSCs and we could obtain ten-hundred million of MSCs. These MSCs were enough for this research
   In medium 50 mL were used 1% (500 µL antibiotic-antimycotic) and 1% (500 µL) nanomycopulitine.

3) As for the figures, we need more. I also think it is important to have figured in the results with histograms or dot - plot of flow cytometry analysis and the evidence of demonstration of the pluripotency through the photographs of the trilineage differentiation of these particular cellular type: the Synovial Membrane Mesenchymal stem cells.

Answer:

This research, we didn't have dot-plot flowcytometry. We have mentioned in the method section that our research using RT-qPCR and ELISA. The dot plot of flow cytometry has been published at our paper which we cited in no 26 (Marlina M, Rahmadian R, Armenia, Widowati W, Rizal R, Kusuma HSW, et al., 2019. Isolation, characterization, proliferation, and differentiation of synovial membrane-derived mesenchymal stem cells (SM-MSCs) from osteoarthritis patients. Mol Cell Biomed Sci.). This paper characterized the phenotype of SM-MSCs using flowcytometry, proliferation capacity and differentiation capacity of trilineage differentiation

4) There is a need to improve the image quality; in the abscissa, the graphics are barely visible, poor quality.

Answer:

Thank you for your suggestion, I change to better image

5) All figures need their number to the identifier.
Answer:

All figures has been number identifier.

Reviewer #2 (Comments to the Authors (Required)):

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Answer: The title of manuscript has been changed as suggested.

SMMSCs-CM was potential for OA therapy and SMMSCs induced by IGF could increase the potential of SMMSCs-CM

2: whether the authors should add a group of OA cell models induced by IGF-1 alone as a control can better explain the significance of co-culture of IGF-1 and SMSCs-CM.

Answer: Thank you for your advice,

IGF-1 to increase the growth factor (BMP2, TGFB1, FGF18) in SMMSCs-CM which this growth factor are important for OA therapy. We didn't induce CHOON002 using IGF1 because to make OA cell model as inflammation cells we induced CHOON002 using IL1B so IGF to induce growth factor in SMMSCs and IL1B to induce inflammation in CHOON002.

Moreover, we only focused the comparison of IGF-induced SMMSCs-CM and SMMSCs-CM-non induced IGF1 on OA model (IL1B-CHOON002)

3: if conditions permit, the addition of a set of Western-blot experiments in figure3 (markers of metalloproteinases) and figure4 (markers of cartilage hypertrophy) may be more persuasive.

Answer: Thank you for your advice, but we apologize we don't have data about Western Blot experiment. Our research method were ELISA and RTqPCR.

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Answer:

4) There is a need to improve the image quality; in the abscissa, the graphics are barely visible, poor quality.

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Answer:

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Answer: The title of manuscript has been changed as suggested.

2: whether the authors should add a group of OA cell models induced by IGF-1 alone as a control can better explain the significance of co-culture of IGF-1 and SMSCs-CM.

Answer: Thank you for your advice, but in our study not using that control (IL1β-CHON002 induced by IGF-1) because it is enough using normal cell control and IL1β-CHON002 (OA cells

model). Moreover, we only focused the comparison of SMMSCs-CM-induced IGF1 and SMMSCs-CM- non induced IGF1.

3: if conditions permit, the addition of a set of Western-blot experiments in figure3 (markers of metalloproteinases) and figure4 (markers of cartilage hypertrophy) may be more persuasive.

Answer: Thank you for your advice, but we apologize we don't have data about Western Blot experiment.

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EDITORIAL CERTIFICATE

This document certifies that the manuscript listed below was edited for proper English languange, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at PROSAINS.

Manuscript Title:

Conditioned Medium of Synovial IGF1-Induced Membrane Mesenchymal Stem Cells Increases Chondrogenic and Chondroprotective Markers in Inflammatory Chondrocyte

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Date Issued:

5 April 2021

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