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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 63664

Title: Hypoxia-inducible factor-1α–mediated upregulation of CD99 promotes the proliferation of placental mesenchymal stem cells by regulating ERK1/2

Reviewer's code: 03472014
Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Senior Lecturer
Reviewer's Country/Territory: Malaysia
Author's Country/Territory: China

Manuscript submission date: 2021-02-01
Reviewer chosen by: AI Technique
Reviewer accepted review: 2021-02-02 00:45
Reviewer performed review: 2021-02-02 08:44
Review time: 7 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Authors have reported on HIF1α–mediated upregulation of CD99 promotes the proliferation of MSCs by regulating ERK 1/2 pathways. It has a scientific merit and contribute to the understanding on MSC biology.

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 63664

Title: Hypoxia-inducible factor-1α–mediated upregulation of CD99 promotes the proliferation of placental mesenchymal stem cells by regulating ERK1/2

Reviewer's code: 03814168
Position: Editorial Board
Academic degree: PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Pakistan

Author's Country/Territory: China

Manuscript submission date: 2021-02-01

Reviewer chosen by: Ya-Juan Ma

Reviewer accepted review: 2021-02-03 05:02

Reviewer performed review: 2021-02-08 10:32

Review time: 5 Days and 5 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

The manuscript entitled as "Hypoxia-Inducible Factor-1α–Mediated Upregulation of CD99 Promotes the Proliferation of Mesenchymal Stem Cells by Regulating ERK ½" cover an important aspect of stem cells proliferation. The experiments were finely designed and executed with conclusion. However, there are few minor issues which need to be addressed. 1. Language need to be improved. 2. For characterization of MSCs, chondrogenic differentiation is missing. 3. In figure 1A the western blot results need to be quantified. 4. In figure 1B need to be shown that if the data is significant at day 4 only, on other day if it is non-significant, it need to be mentioned. 5. Scale bar should be added at figure 1C. 6. Figure 4 and Figure 5 are exactly same; I think this may be a technical error. Authors need to correct it. 7. Housekeeping protein need to be added in figure 4 for western blot.

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 63664

Title: Hypoxia-inducible factor-1α–mediated upregulation of CD99 promotes the proliferation of placental mesenchymal stem cells by regulating ERK1/2

Reviewer's code: 02567328
Position: Editorial Board
Academic degree: PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

Manuscript submission date: 2021-02-01

Reviewer chosen by: Ya-Juan Ma

Reviewer accepted review: 2021-02-02 10:39

Reviewer performed review: 2021-02-17 17:28

Review time: 15 Days and 6 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

- In title “Hypoxia-Inducible Factor-1α–Mediated Upregulation of CD99 Promotes the Proliferation of Mesenchymal Stem Cells by Regulating ERK ½” should refer to the stem cells used in the experiments (that is) and not use the generic term Mesenchymal Stem Cells - In the Abstract the authors state “Transcriptome profiling of MSCs under hypoxia was performed by RNA-sequencing”. Specify the type of MSC examined - In the abstract the authors indicate only hP-MSCs. hUC-MSC are used only in the paragraph "Hypoxia induces CD99 expression via HIF-1α" for analyzed their mRNA profile comparing with hP-MSCs profile. There are two possibilities: 1) delete hUC-MSC resuts from this paragraph and in the materials and methods; 2) do all the experiments performed for hP-MSCs also for hUC-MSCs. It is necessary to make a choice for the validity of the manuscript - In Material and Methods there is a paragraph named “Isolation and hypoxic culture of MSCs”. Please indicate the type of MSCs isolated - Why did the authors use PD98059 as ERK inhibitor? There are other more recent and specific inhibitors. PD98059 is also a reversible inhibitor - Why did the authors evaluate CCNE1, CCNA2, CDK2 and p21 in the paragraph "Hypoxia promotes hP - MSC proliferation by modulating cell-cycle progression"? CCNE1 gene encodes cyclin E which controls G1 / S. CCNA2 gene encodes cyclin A2, controls G1 / S and G2 / M transition. CDK2 gene encodes for Cdk2v acts as G1 / S checkpoint control. p21 is a potent inhibitor of cyclin-dependent kinases (CKI) and regulates cell cycle progression at the checkpoint between the G1 and S phases. There is no evaluation of factors that regulate the G2 / M phase. Also why did they label proteins with the names of genes? It doesn't seem appropriate. - The authors evaluate the protein level of CD99 by immunostaining. Using this method, only a qualitative and not a quantitative analysis is carried out. To evaluate the protein level it is necessary to carry out Western Blot

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experiments with subsequent quantization - In figures 4A, 5A, 5C, 6A and 6C a generic p-ERK and ERK cannot be written. It is necessary to specify in the western blots which band corresponds to ERK1 and which to ERK2. - The concentration of PD98059 used in the different experiments is not specified. Please specify - In figure 6C, in the presence of the inhibitor, an important residual ERK2 phosphorylation is observed. In my opinion as the inhibition is not total the subsequent results are not reliable. - In the paragraph “Hypoxia-induced CD99 regulates hP-MSC proliferation via the MAPK/ERK pathway”, the authors state “Western blotting and immunofluorescenceanalysis revealed that hypoxia-induced phosphorylation of ERK1 and ERK2 decreased as the expression of CD99 decreased (Fig. 6A, B)”. But this sentence is unclear as in the western Blot 6A siCD99 # 1 is indicated and do not correspond to the text . Rewrite the sentence - The authors used a kit to separate Nuclear and Cytoplasmic Proteins. There is the possibility of contamination between the two fractions. It is necessary to demonstrate that the nuclear fraction is only nuclear otherwise the results obtained are not valid

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Stem Cells

Manuscript NO: 63664

Title: Hypoxia-inducible factor-1α–mediated upregulation of CD99 promotes the proliferation of placental mesenchymal stem cells by regulating ERK1/2

Reviewer's code: 03814168
Position: Editorial Board
Academic degree: PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Pakistan

Author's Country/Territory: China

Manuscript submission date: 2021-02-01

Reviewer chosen by: Chen-Chen Gao

Reviewer accepted review: 2021-03-12 03:52

Reviewer performed review: 2021-03-12 04:09

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

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The revised version of manuscript is improved. All the queries and concerns are successfully addressed in revised version. Therefore, the manuscript is accepted in present form.

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Stem Cells

Manuscript NO: 63664

Title: Hypoxia-inducible factor-1α–mediated upregulation of CD99 promotes the proliferation of placental mesenchymal stem cells by regulating ERK1/2

Reviewer's code: 02567328
Position: Editorial Board
Academic degree: PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

Manuscript submission date: 2021-02-01

Reviewer chosen by: Chen-Chen Gao

Reviewer accepted review: 2021-03-12 08:33

Reviewer performed review: 2021-03-14 14:51

Review time: 2 Days and 6 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

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I thank the authors for their exhaustive answers to my questions and for making the required changes. I still have some observation: - Answer 3: The authors did not answer my question. But is it necessary to have hUC-MSCs as a control for CD99? If it is not necessary please delete it from the paragraph and from the materials and methods. If, on the other hand, it is necessary to explain why - Answer 8: In this answer the authors state" We have specified ERK1 and ERK2 band in the western blots results in revised Figure 4-6". But in Figure 4 there is no ERK1/ERK2 western blot. As reported by Reviewer #2, Figure 4 and Figure 5 are exactly same. The authors recognized the mistake and inserted the right figure. In the answer to my question, it would have been appropriate to underline that the corrections concerned fig 5 and 6 as there was an error for figure 4 - Answer 10: Thanks for the answer, but I believe that the observed residue phosphorylation for ERK1 and ERK2, may have its own relevance in the conclusions drawn from the experiment. However this is my opinion and I accept your answer