

PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 78888

Title: TNF- α inhibition restores matrix formation by hADSCs in the late stage of chondrogenic differentiation

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02461627

Position: Peer Reviewer

Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: United Arab Emirates

Author's Country/Territory: China

Manuscript submission date: 2022-07-20

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-07-20 15:37

Reviewer performed review: 2022-07-25 16:36

Review time: 5 Days

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input checked="" type="radio"/>] Anonymous [<input type="radio"/>] Onymous Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No
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SPECIFIC COMMENTS TO AUTHORS

The manuscript entitled “Etanercept restores the matrix formation of hADSCs in the late stage of chondrogenic differentiation” authored by Wan et al showed a pattern of combining stem cell therapy and targeted anti-inflammatory drugs to treat cartilage damage diseases. Authors then argued that the adverse effects of in vitro-induced chondrogenic differentiation can be eliminated, and the therapeutic effect of hADSCs maximized through specific targeted drugs. Data from the following studies provides a broader perspective of inflammatory mechanism and treatments and should be integrated in the introduction: PMID: 29959408, PMID: 35568708, PMID: 17151319, PMID: 17151316, <http://dx.doi.org/10.4236/jdm.2011.13006>, PMID: 15362483. It could have been interesting to compare the current results with the effects of other inhibitor that does not target TNF. Other comments

- Proofreading is required.
- Who exactly has waived “patient consent”?
- The abstract is not coherent and must be re-written using shorter and more clear sentences.
- As most of the “core tip” is a copy/paste from the abstract, the core tip must be rephrased too and preferably be reworded differently from the abstract.
- What is meant by “P3 hADSCs”?
- All abbreviations must be reviewed.

In figure 1, were those cells “P3 hADSCs”, P1 or P2? This need to be clarified and clearly stated in the manuscript. How many times have all presented experiments been repeated?

- Fig 1c need to be better labelled and be consistent with data presented in the result section.
- All western blots need to be quantified and their uncropped gels added as supplementary data.
- Quantify the scratch assay in fig 2c.
- The list of references needs to be diversified and more inclusive. If considered, the following studies would help addressing that concern and provide more insights into molecular

bases of anti-inflammatory and proapoptotic mechanisms: PMID: 34662244, PMID:
35211395, PMID: 35517830, PMID: 35740022, PMID: 35177980, PMID: 33255507,
<https://doi.org/10.1039/D0NA00958J>, 10.1097/HM9.0000000000000008,
<https://doi.org/10.1186/s41936-020-00177-9>,
<https://doi.org/10.1186/s41936-021-00251-w>.

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06232300

Position: Peer Reviewer

Academic degree: PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: China

Author's Country/Territory: China

Manuscript submission date: 2022-07-20

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-07-22 08:03

Reviewer performed review: 2022-08-03 07:28

Review time: 11 Days and 23 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

The article showed that the expression level of tumor necrosis factor- α (TNF- α) was increased during the in vitro chondrogenic differentiation of human adipose-derived stem cells (hADSCs), which then bound to the receptor and activated the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway, leading to a decline in the capacity of cartilage matrix synthesis and secretion. The conclusion was verified by blocking the above process and restoring the matrix formation significantly with using etanercept (1 μ g/mL), an inhibitor of TNF- α . The results are meaningful, while there are some concerns as follows: 1) Besides etanercept, another one of the TNF- α inhibitors should be used to investigate the effect on the chondrogenic differentiation and the modulation of TNF- α in the NF- κ B pathways. And so did at least the two dosages of TNF- α inhibitors. 2) The effect of TNF- α inhibitors on the expression of NF- κ B and MMP3 proteins in the control medium for chondrogenic differentiation of hADSCs should be studied and compared with the other groups. 3) The statistic analysis should be described more clearly as one to one correspondence. 4) In Figure 2, what were the changes in Aggrecan and COL2 at 14d when compared with control or those at 7d? The similar problem was also found in Figure 4a. 5) In Figure 3a, the expression of MMP3 in GM group was at 7d or 14d? In this figure, the control group should be set at 7d and 14d respectively. 6) In Figure 5, semi quantitative WB analysis of MMP3 and NF- κ B should be carried out. 7) The author presented that IL-1 β alone did not affect the expression of TNF- α or MMP-3 in hADSCs while it upregulated the expression of MMP-3 in the presence of a chondrogenic differentiation medium. This results should be discussed in detail.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: United Arab Emirates

Author's Country/Territory: China

Manuscript submission date: 2022-07-20

Reviewer chosen by: Ze-Mao Gong

Reviewer accepted review: 2022-10-09 16:46

Reviewer performed review: 2022-10-09 17:00

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

none