



PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 64768

Title: The anti-fibrotic effect of adipose-derived stem cells (ADSCs) on fibrotic scars

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02567167

Position: Peer Reviewer

Academic degree: PhD

Professional title: Research Scientist

Reviewer's Country/Territory: Spain

Author's Country/Territory: Belgium

Manuscript submission date: 2021-02-23

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-02-23 20:12

Reviewer performed review: 2021-03-06 23:15

Review time: 11 Days and 3 Hours

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 Grade E: Do not publish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 checked="" type="checkbox"/> Grade A: Priority publishing <input 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 checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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

SPECIFIC COMMENTS TO AUTHORS

The review article entitled "The anti-fibrotic effect of adipose-derived stem cells (ADSCs) on fibrotic scars after radiotherapy" by Sophie Vanderstichele and Jan Jeroen Vranckx, describes how ADSCs can reduce fibrotic scar formation. The article shows how ADSCs can act through different mechanisms. These include its paracrine effect, modulation of the expression of MMPs, TIMPs and TGF- β 1, its immunomodulatory and pro-angiogenic effect. The article is well structured and provides very interesting information on the potential of ADSCs to reduce fibrotic scars. Remarks: 1- On page 13, in the section Pro-angiogenic effect of fat grafting and ADSCs, the authors write: "In response to entering a hypoxic environment, ADSCs release bFGF, hypoxia-inducing factor-1 α (HIF-1 α), and insulin-like growth factor-1 (IGF-1)...". Is HIF-1 α released?. I think in the case of HIF-1 α , it would be more correct to say that it is activated or that its expression is increased. 2- Due to the relationship with the article, the authors should evaluate whether to include the following reference in the paper: "Ejaz A, et al. Adipose-Derived Stem Cell Therapy Ameliorates Ionizing Irradiation Fibrosis via Hepatocyte Growth Factor-Mediated Transforming Growth Factor- β Downregulation and Recruitment of Bone Marrow Cells. *Stem Cells*. 2019 Jun;37(6):791-802. doi: 10.1002/stem.3000.". 3- The authors highlight that the pro-angiogenic capacity of ADSCs is one of the mechanisms of their anti-fibrotic effect. However, in some cases, such as liver fibrosis, angiogenesis promotes fibrosis (e.g. Zadorozhna M, Di Gioia S, Conese M, Mangieri D. Neovascularization is a key feature of liver fibrosis progression: anti-angiogenesis as an innovative way of liver fibrosis treatment. *Mol Biol Rep*. 2020 Mar;47(3):2279-2288. doi: 10.1007/s11033-020-05290-0.). It would be desirable that the authors discuss this.



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Peer-review model: Single blind

Reviewer's code: 03550310

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Academic Research, Associate Professor, Executive Vice President

Reviewer's Country/Territory: Egypt

Author's Country/Territory: Belgium

Manuscript submission date: 2021-02-23

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-02-23 21:29

Reviewer performed review: 2021-03-10 19:00

Review time: 14 Days and 21 Hours

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 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
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Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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

SPECIFIC COMMENTS TO AUTHORS

This review has elucidated the anti-fibrotic effect of ADSCs on fibrotic scars in a comprehensive and organized manner, yet I have some comments to the authors; 1- The title and aim of the review focused on the fibrotic scars after radiotherapy, yet the review elaborated the mechanisms leading to fibrosis in general with no specification for that after radiotherapy, which if has no specific features than it should be omitted from the title , aim ...etc 2- Authors mentioned that they included review articles in writing this systematic review. There are some reviews related to the work but not referred to in the manuscript, for example Shukla, Lipi et al. "Adipose-derived stem cells in radiotherapy injury: a new frontier." *Frontiers in surgery* vol. 2 1. 28 Jan. 2015, doi:10.3389/fsurg.2015.00001 3- As a review article, I suggest mentioning the limitations of using the ADSCs as well, highlighting the new era of using the secretome of these cells (exosomes) to overcome cell transplantation limitations. 4- In page 6 last paragraph, (Histological patterns do not only reflect the increased ECM deposition but also the enhanced inflammation, through an increase of interleukine-6 (IL-6) and interleukine-8 (IL-8), and reducedetc). the increase of IL6 and IL8 are not a histological finding , so re-writing this paragraph should be considered. 5- (As said above) is an Informal expression which have been used more than once in the manuscrip , please delete. 6- A spelling mistake should be corrected in page 7 (The homeostasis of the ECM is a well-regulated process influenced by a variety of actors and is subjected.....) please correct it 7- MMP2, MMP9 recently proved to have a role in angiogenesis , authors can search recent publications and include this role in the manuscript instead of mentioning that their role is unclear. 8- Keywords are missing



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Peer-review model: Single blind

Reviewer's code: 00503243

Position: Editor-in-Chief

Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: Belgium

Manuscript submission date: 2021-02-23

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Reviewer accepted review: 2021-03-08 13:09

Reviewer performed review: 2021-03-20 09:20

Review time: 11 Days and 20 Hours

Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent <input 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
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Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This is an excellent and well written manuscript on the effect of stem cells derived from adipose tissue on fibrosis induced by several mechanisms. In particular the authors highlight the anti fibrotic and pro angiogenic effects and the multiple pathways involved. I do not have any comment and only would like to congratulate with the authors. In addition, literature is complete and updated.