

Dear Editor,

Thank you for carefully reviewing our manuscript previously titled “Exosomes from circ-Astn1-modified adipose-derived mesenchymal stem cells enhance wound healing through miR-138-5p/SIRT1/FOXO1 axis regulation” for possible publication in the World Journal of Stem Cells. We are grateful to you and your reviewers for their constructive critique. We have revised the manuscript, highlighting our revisions in red. And have attached point-by-point responses detailing how we have revised the manuscript in response to the reviewers' comments below.

Thank you for your consideration and further review of our manuscript. Please do not hesitate to contact us with any further questions or recommendations.

Yours Sincerely,

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: In the work titled “Exosomes from circ-Astn1-modified adipose-derived mesenchymal stem cells enhance wound healing through miR-138-5p/SIRT1/FOXO1 axis regulation” by Zhi Wang etc., the authors revealed circ-Astn1 promoted adipose-derived mesenchymal stem cell-exosomes therapeutic effect and thus improved wound healing in diabetes via miR-138-5p absorption and SIRT1 upregulation. The study is logically designed, the idea is new and very interesting.

Although, there are several concerns that need to be addressed. Comments:

1. More work should be added in the Discussion section.

Response: Thank you for your important comment. It have been added.

2. An in-depth mechanism study is lack in this work. The authors should add more mechanism study in the manuscript, or add your research plan at least.

Response: Thank you for your insightful comment. It have been added.

3. It is better to add more work about exosomes, in the introduction section. More references about the mechanism of exosomes should be cited, “Exosomes as mediators of intercellular crosstalk in metabolism”, “Exosomes Regulate the Epithelial-Mesenchymal Transition in Cancer” and “The biology, function, and biomedical applications of exosomes”, for example, or any other similar references.

Response: This point is well taken. It have been added.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: The manuscript entitled “Exosomes from circ-Astn1-modified adipose-derived mesenchymal stem cells enhance wound healing through miR-138-5p/SIRT1/FOXO1 axis regulation” and authored by Wang et al concluded that circ-Astn1 promoted ADSC-exosomes therapeutic effect and thus improved wound healing in diabetes via miR-138-5p absorption and SIRT1 upregulation. Based on our data, we advocate targeting the circ-Astn1/miR-138-5p/SIRT1 axis as potential therapeutic alternative regarding diabetic ulcers. The following studies present insights into wound healing, diabetes developed in animal model and the use of stem cells in diabetes, should be considered for integration: PMID: 33338743, PMID: 32837538, PMID: 29959408, PMID: 21258076, <https://www.scirp.org/journal/paperinformation.aspx?paperid=7085>, PMID: 17151316, PMID: 17151319, PMID: 32460808, PMID: 33782460, PMID: 34202689, PMID: 33255507, <https://doi.org/10.1186/s41936-020-00177-9>, PMID: 34639131, PMID: 26034352, <https://doi.org/10.4236/ajps.2018.96091>, PMID: 22812448. One concern is the lacking of proper in vitro system to further analyze the molecular mechanism of wound healing? Other comments • Careful proofreading is ABSOLUTELY mandatory. • Animal research ethics approval number is not clear. • How exactly were the examined animals euthanized? • References list need to be updated. Some of the references suggested here can help with that too.

Response: Animal Care and Use Committee of Peking Union Medical College Hospital approved the investigation protocol (No: XHDW-2020-01). We carried out all postoperative animal care along with surgical interventions following NIH Guide for Care and Use of Laboratory Animals. All surgery and euthanasia were performed under sodium pentobarbital anesthesia (30 mg/kg) by intraperitoneal injection, and all efforts were made to minimize suffering. The reference you suggestion were added in the introduction. Thank you very much.

Reviewer #3:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: Dear Author, 1. Excellent study. 2. In the introduction part you had mentioned that because of diabetes \$327 Billion , so how ur study could possibly decrease this huge financial burden in near future. 3. How this ADSC therapy can possibly helps in preventing diabetic nephropathy and retinopathy also.

Response: Thank you for your constructive comment. Therapy using ADSCs is developing into new therapeutic option to improve diabetic wound healing, and autologous stem cell transplantation reduces the cost of drug development, which in turn reduces financial costs. But the mechanism is not clear.

Previous studies have been found that exosome secreted from ADSCs attenuates diabetic nephropathy by promoting autophagy flux and inhibiting apoptosis in podocyte. It have been added in the introduction. But their were no ADSC therapy for retinopathy.

4. It's future impacts on quality of life and in paving way for such multicentric studies all over the globe. Thanks

Response: Thank you for your valuable comment. It have been added. The abundance and the simple methods of sampling of ADSCs Exos make it safer against trauma and other adverse reactions.