

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.

## Journal editor-in-chief review report

### ROUND 1

Dear Dr. Wang,

The following is the second round of comments from the journal editor in chief. Please review and reply for revisions.

#### EIC Specific comments on R2

1) Page 9: "Diabetic wound induction We utilized Balb/c mice and induced diabetes through single intraperitoneal injection of 60 mg/kg streptozotocin (STZ)" [add a before single].

**Response :** It have been added.

2) MATERIALS AND METHODS: I wanted to bring to your attention that the writing style in the entire section appears to be a mix of passive and active voice, which may potentially create confusion for the reader. In current scientific publications, it is generally preferred to use passive voice. However, if the section was intended to be written in passive voice to align with the conventions of scientific writing, it may be worth revising the active voice sentences to ensure consistency throughout. It is important to consider the implications that the use of passive voice was suggested by someone else, whereas the use of active voice may have been a choice made by the authors. Would it be possible to revise the section to ensure consistency and clarity?

**Response:** Thank your comments, we have been revised as your suggestion.

3) Page 13: "Transmission electron microscopy revealed that ADSC Exos had spherical or cup-shaped morphology with [a] diameter ranging from 50 to 120 nm (Figure 1J) as previously reported[21]."

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

Page 14: "treatment with Exos containing high levels of circ-Astn1 were [was] more effective in promoting angiogenesis of EPCs under HG conditions (Figure 2G-J)."

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

5) Page 17: ", our research indicateds [indicates] that Exos derived from circ-Astn1-modified ADSCs enhanced wound healing"

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

6) Page 17: "Our study verified the therapeutic effects of circ-Astn1-Exos on a [an] STZ-induced diabetic wound healing model."

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

Page 18: "derived mesenchymal stem cells (ADSCs) exhibit [the] potential to improve endothelial cell function along with the wound healing process."

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

Best regards,

## ROUND 2

Dear Dr. Wang,

The following is the second round of comments from the journal editor in chief. Please review and reply for revisions.

### EIC Specific comments on R2

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