

Dear Editor and Reviewers,

Thanks very much for taking your time to review this manuscript. I really appreciate all your comments and suggestions! Your suggestions have enabled us to improve our work. Based on the instructions provided in your letter, we uploaded the file of the revised manuscript. Appended to this letter is our point-by-point response to the comments raised by the reviewers. The comments are reproduced and our responses are given directly afterward in a different color (red). We would like also to thank you for allowing us to resubmit a revised copy of the manuscript. Furthermore, we would like to show the details as follow:

**The Editorial Office's comments:**

Q1. The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company.

**Response:** We apologize for the language problems in the original manuscript. We have tried our best to polish the language in the revised manuscript. we have provided the English Language Certificate issued by a professional English language editing company. The professional English language editing companies you recommended is also very good, and We will consider using it in my next job.

Q2. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript.

**Response:** We think this is an excellent suggestion. We have read the latest cutting-edge research results, and in the revision to supplement and improve.

Q3. Authors are advised to apply a new tool, the Reference Citation Analysis (RCA).

**Response:** We really appreciate recommending the use of RCA tools. Combined with

the content of the article and the RCA tool to consult the literature, we have supplemented and improved the content.

Q4. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023.

**Response:** We are very sorry that our pictures cannot be edited by PPT directly. Therefore, we provide links to web addresses (in which all the components are removable and editable) and put them in a PowerPoint file. The author adds the following copyright information to the bottom right of the PPT image :copyright©the author (s) 2023.

Q5. The editor would like to see addition of figure(s) to summarize key points in the revision.

**Response:** We are grateful for the suggestion. As suggested by the reviewer, we have added Figure 2 Sources and Potential Function for stroke of Mesenchymal Stromal Cells.

**Reviewer #1:**

Q1. What does 'cell membrane a' mean in page 6 / lane 11?

**Response:** We sincerely appreciate the valuable comments. We feel sorry for our carelessness. In our resubmitted manuscript, the typo is revised. we have corrected the 'cell membrane a' into 'cell membrane'. Thanks for your correction.

Q2. In the neuroprotection concept, controlling inflammation may be a major reason for improving ischemic stroke. However, the authors also need to mention the controlling after ischemic stroke including neurogenesis and angiogenesis.

**Response:** Thank you for your suggestion. As suggested by reviewer, we have added the suggested content to the manuscript in page4, last paragraph.

Q3. The signaling pathway following the explanation of the chapter ‘MSC-EVS REGULATE INFLAMMATORY RESPONSE IN ISCHEMIC STROKE TREATMENT’ seems to be a description of factors related to inflammation. However, the author did not mention what criteria of these factors were selected for and what the order of presentation means. We suggest that the authors mention about it. In addition, the factors enclosed in MSC-EVs are diverse, but the reason for presenting miRNAs in particular has not been clearly explained.

**Response:** We deeply appreciate the reviewer’s suggestion. We have provided what criteria of these factors were selected for and what the order of presentation means . Furthermore, according to the reviewer’s comment, we have provided more details to describe the possible reasons in page8, first paragraph.

Q4. miRNAs associated with MSC-EVs and activated Treg cells were not presented. Have the authors ever checked?

**Response:** Thank you for the suggestion. We have added the information required as explained in page14, first paragraph.

**Reviewer #2:**

Q1. Page 4, last paragraph: “Brain cell death after stroke can lead to a series of pathological processes, including cell energy failure, neuronal apoptosis, leukocyte infiltration, inflammatory immune response, tight junction (TJ) protein breakage and degradation, BBB destruction, and increased permeability.”, references will be needed.

**Response:** We are grateful for the suggestion. As suggested by the reviewer, we have added more references to support this idea (Reference 13,14).

Q2. Page 5, 2nd paragraph, more references will be needed regarding the M1 and M2 and their functions.

**Response:** We sincerely appreciate the valuable comments. We have checked the literature carefully and added more references to the M1 and M2 and their functions on the page 5 / lane 16-21 of the revised manuscript.

Q3. Page 6, 1st paragraph, more references will be needed about MSCs including their types and functions.

**Response:** Thanks for your suggestion. We have checked the literature carefully and added more references to MSCs including their types and functions on the page 6 / lane 9-15 of the revised manuscript.

**Reviewer #3:**

None.

Thank you very much for your attention and time. Look forward to hearing from you.

Yours Sincerely,

Na Chen

21 Apr, 2023

Henan University of Chinese Medicine