

2020/05/06

Dear Editor in-chief,

Thank you for the professional and kind comments on our paper, which was invited for submission to World Journal of Stem Cells (ID: 03893437). According to comments of all reviewers, we have carefully revised the manuscript. The revised parts have been marked in red in the revised paper. Please check the following details point by point.

**Reviewer 1:**

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Additional references should be added (Carl Randall Harrell et al., Cells 2019, 8, 1605; doi:10.3390/cells8121605; Vito Pistoia and Lizzia Raffaghello, International Immunology, Vol. 29, No. 2, pp. 49–58 doi:10.1093/intimm/dxx008. Moreover, should offer to readers some hypothesis regarding their possible use in therapeutic strategies. Moreover, the authors should prepare a table describing the factors and signaling molecules stimulated by mesenchymal stem cells derived extracellular vesicles and modify the figures to offer a more complete scenario on data.

**Response to Reviewer 1:** Thank you for the professional and kind comments on our article. We have carefully revised the paper according to your advice. We have added some appropriate reference and offered the hypothesis based on current studies. We prepare a table for description of MSC-EVs and target molecules in autoimmune related diseases after summarizing data we had obtained (Table 1). Please check details in the revised paper. Thank you very much.

**Reviewer 2:**

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The manuscript entitled “Role of Mesenchymal Stem

Cells Derived Extracellular Vesicles in Autoimmunity: a Systematic Review” describes and focus on the identification, characteristics, immunomodulatory function and underlying mechanism of MSC-EVs in autoimmunity related diseases. Mesenchymal stem cells (MSCs) have been reported to possess immune regulatory effects in innate and adaptive immune reactions. MSCs can mediate intercellular communications by releasing extracellular vesicles (EVs), which deliver functional molecules to targeted cells. MSCs derived EVs (MSC-EVs) confer altering effects on many immune cells, including T lymphocytes, B lymphocytes, natural killer (NK) cells, dendritic cells (DCs) and macrophages. A large number of studies have suggested MSC-EVs participate in regulating autoimmunity related diseases. Many validated EVs-delivered molecules have been identified as key biomarkers, such as proteins, lipids, and nucleotides. Some EVs-encapsulated functional molecules can serve as promising therapeutic targets particularly for autoimmune disease. It suggests authors to provide the followings for easy comprehension. (i)Providing the table for presenting the effect of MSC-EVs on the immune system (MSC source / Target cell / MSC-EVs effect / Refences.....) (ii)Providing the table for presenting the MSC-EVs derived molecules (factors) and/or mechanisms that act as a role in the immune modulation. (iii)Providing the table for presenting the potential therapeutic application of MSC-EVs for disease models.

**Response to Reviewer 2:** Thank you very much for the high appreciated and professional comments on our paper. We have carefully revised the paper based on your suggestions. We have provided the table to describe the immunomodulation of MSC-EVs on the target immune cell and offer biomarkers may be novel biotargets for development of targeted drug of autoimmune related diseases (Table 1).

**Reviewer 3:**

Scientific Quality: Grade C (Good)

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

Conclusion: Minor revision

Specific Comments to Authors: The overall concept of the manuscript is very informative. Title reflect the subject of the manuscript. Abstract is in the summarized

form and key words relate to the topic. In introduction, manuscript needs to be describe some other chronic autoimmune disease, more background related to the topic, recent development and significance of the study. In page 4, line 25, check the spelling of urine.

**Response to Reviewer 3:** Thank you very much for the kind reminding. We have corrected the spelling of urine. Moreover, we have added the introduction for chronic autoimmune diseases and the relationship between MSC-EVs and autoimmune diseases.

Thank you very much again for the professional and kind comments on our paper. Due to the great contribution of Xiaoling Liu for our revised paper, all authors have agreed to add her to co-author in our revised paper. If there are any other questions, please contact us by email as soon as possible. Thank you again for the professional and kind comments on the article.

Best regards,

Jinghua Wang et al.