

Mar. 9th, 2021

Re: Manuscript Number: 64069

Dear editor of *World Journal of Stem Cells*,

Enclosed is our revised manuscript entitled “Therapeutic Prospects of Mesenchymal Stem/stromal Cells in COVID-19 Infected Pulmonary Diseases: From Bench to Bedside” (Manuscript Number: 64069). We greatly appreciate the insights provided by the reviewers and the editor. The manuscript has been carefully revised according to their comments. We believe the new data provided should suffice to address the concerns from the reviewers. The following are our point-by-point responses to the reviewers’ comments.

## **Response to Reviewer 1**

**Reviewers' comments:** This is a very important study on the effect of MSC therapy in COVID-19 treatment. The relationship between the result of the influenza virus H1N1-induced mice model and MSC-derived extracellular vesicle may be described more in detail and focused in terms of the role of MSCs, in around lines 143 to 149. It may be discussed what potential components in MSC-derived extracellular vesicle are critical for COVID-19 treatment.

**Answer:** We greatly appreciate the positive comments as well as the insightful suggestions from the reviewer. According to the comments, we have carefully added essential descriptions upon the relationship between the result of the influenza virus H1N1-induced mice model and MSC-derived extracellular vesicle. Meanwhile, we have also discussed the potential components in MSC-derived extracellular vesicle that might be critical for COVID-19 treatment as well. We believe our revised manuscript significantly strengthen the manuscript and should suffice to address the concerns. In details, we added the following descriptions in the revised manuscript and labeled in red, “Studies on the underlying mechanism suggested that MSC-EVs with anti-inflammatory and anti-influenza properties could incorporate into the H1N1-infected lung epithelial cells and suppress influenza virus replication and virus-induced apoptosis as well as the virus-induced accumulation of proinflammatory cytokines. Interestingly, by conducting pre-incubation with RNase enzyme, Khatri *et al* found that the anti-influenza activity of MSC-EVs was abrogated,

which indicated the pivotal role of transferred RNAs from MSC-EVs to H1N1-infected lung lesions[1]. Thus, MSC-EVs were suffice to mimic the beneficial effects of MSCs and attenuate ALI caused by influenza virus and the newly generated COVID-19 via simultaneously restraining virus replication and the inflammatory response.”

### **References:**

1. Khatri M, Richardson LA, Meulia T: **Mesenchymal stem cell-derived extracellular vesicles attenuate influenza virus-induced acute lung injury in a pig model.** *Stem Cell Res Ther* 2018, **9**(1):17.