

Answering Reviewers

For the reviewer (00532996) in India:

Thank you for your admission about the scientific quality and language quality of my manuscript and give me the opportunity to revise it. All of your suggestions are meaningful and worth to think deeply. I'll give you my answers according to your valuable suggestions.

1. About the predisposing conditions and causative factors, I have added in the introduction, as for the incidence, prevalence and frequency, only liver cirrhosis and liver cancer have these statistical data and there are no epidemiological studies of liver fibrosis at present. Moreover, we will pay close attention to the research in this field. 2. The table about clinical trials using hUC-MSCs has been inserted in my manuscript and the Internet site about clinical trials are provided. 3. As for ethical issues, many references cited in my manuscript have said that the umbilical cord is a medical waste and there are no substantial ethics challenges. Maybe there are some limitations in using umbilical cord but I have not found a reference mentioned about it. 4. The four latest relevant references are in good quality and I have read them when I drafted my manuscript. There are indeed many latest relevant references which can be searched. The reason why I didn't cite them at first is that my title is about "human umbilical cord mesenchymal stem cell" and "liver fibrosis", the references which do not meet the title have been excluded. However, the four references indeed can provide some ideas or some directions in the cell-based therapy, so I cite them in front of the introduction.

For the reviewer (02728252) in Egypt:

Your suggestions are very helpful and useful. First of all, my manuscript is indeed to be shorten particularly the part introducing the biological characteristics of hUC-MSCs. According to the suggestion put forward by the editor, a short running title should be added, so I add the running title "From biological characteristics to therapeutic mechanisms" attached to my main title. I suppose the running title could give readers some information about my manuscript. Second, many references have reported the influence of hUC-MSCs in ameliorating liver fibrosis. In addition, a reference suggested that umbilical cord tissue account for 35% of the MSCs in clinical trials for liver disease and this reference has been cited in my manuscript.

Third, the abbreviation has been clarified: 8-OHdG (8-hydroxy-2 deoxyguanosine) and English language editing is conducted by an editorial company.

For the reviewer (02446223) in Italy:

Thank you for your recognition about my manuscript. I have shortened my manuscript about 1,000 words. As for the spelling mistakes, I did find some and corrected them carefully. I'll reread my manuscript carefully again and again to avoid the mistakes which should not exist.

For the reviewer (03471268) in Japan:

Thanks for your review. According to the editor's suggestion, a short running

title has been attached to my main title, expressing my article logic clearly: From biological characteristics to therapeutic mechanisms. Though there are still much unclear points to understand the mechanism, some valuable results *in vivo* and *in vitro* do exist in current situation about the hUC-MSCs in ameliorating liver fibrosis.

The answers which based on your suggestions are as follows:

1. I have shortened this part. 2. Yes! MSCs are distinctly different from ESCs. In our review, we only want to introduce the biomarkers of hUC-MSCs, rather than compare with the biomarkers of ESCs. hUC-MSCs express OCT4, SOX2, and NANOG too, which only means hUC-MSCs are more original stromal stem cells between the embryonic and adult stem cell stages. 3. The transdifferentiation of hUC-MSCs into hepatocyte-like cells is as one of the possible mechanisms studied by a lot of researchers. There are many methods to achieve this aim though not mature. 4. The transdifferentiation stage in hepatocyte-like cells, not yet the real hepatocytes, but there do have many progresses in expressing several characteristics of real hepatocytes. Moreover, transdifferentiation of hUC-MSCs into hepatocyte-like cells is only one of the mechanisms about hUC-MSCs in ameliorating liver fibrosis.

For the reviewer (02446277) in Romania:

Thanks for admitting my manuscript and your careful work. The contents are indeed not matching the title properly. But I add a short running title according to editor's suggestion: From biological characteristics to therapeutic mechanisms. Meanwhile, I have shortened this part of content and I suppose my manuscript would be understood easily. Moreover, I have thought seriously about the aspects you mentioned and these are my answers:

1. As for the abbreviation for proper nouns, we cannot avoid that there are several proper nouns with the same abbreviation. Though hepatic stellate cells (HSC) is easy to be confused, the full name will make it easy to understand the abbreviations. 2. YES! I have added "liver fibrosis" behind MFBLCs. 3 and 4. YES! The spelling mistake has been corrected and I have changed "Gene editing" into "Gene transfection". 5. For the trial numbers, I have created a table titled with "Clinical trials in liver diseases using hUC-MSCs" and the trial numbers were contained in the table.

For the reviewer (02524648) in Spain:

Thank you for admitting my manuscript and its structure. For your major comments, I'll give the answers as follows:

1. The English language editing has been done. 2. Yes! current methods and the solutions have been mentioned in the relative parts, and I just illustrate the unsolved issues as some points of breakthroughs provided for other researchers. 3. I'm optimistic for the current research situation, but we should know what aspects are to be done in the future. From the whole manuscript, we can know what results and issues have been done and what problems and improvements are to be done. 4. About figure 1 and 2, the illustration of the

figures is in the related content of my manuscript. As for the figure 3, I attached a paragraph of text explaining the process of intracellular signal transmission. 5. As for the headings, I have corrected "H" into "h". 6. For the genetic stability, according to Hatlapatka *et al.*, they found a long-term expansion of the cells is optimal in the presence of HS supporting high proliferative potential, a homogenous morphology, **a stable MSC marker expression**, and sustained immunomodulatory properties. Moreover, several references have suggested that hUC-MSCs can maintain stable after sub-cultured. I didn't introduce too much about the genetic stability because of the length of my manuscript. 7. About Weissh^[62] (original) (revised into[66]), it's the same reference as the front. Moreover, the content followed is the illustration of this reference, introducing the biomarkers of hUC-MSCs. Because of the length, I didn't illustrate this reference in detail. 8. The "infected" has been changed into "transfected". 9. The problems inherent to gene editing in hUC-MSCs do exist, just like gene editing in other cells. It is a common problem currently. Besides, my manuscript focuses on "biological characteristics to therapeutic mechanisms". so that I didn't illustrate it in detail. But this is indeed one of the most important problems, I will research and comment on this point in the future 10. The TGF- β /Smad signaling pathway is well-known in the reduction of liver fibrosis. As for the mechanism, we can learn it from the related references as well as the cited references in my manuscript. 11. I have checked out the full name of 8-OHdG. 12. Full name of TBIL has been indicated below the table added.

For the reviewer (03814168) in Pakistan:

Thanks for admitting my manuscript both in scientific quality and in language quality. About the signaling pathway, I mainly use them in the paracrine mechanism. As for the Wnt and Notch pathway, no references have been searched by me about hUC-MSCs but I did cite some references to provide a few ideas for researchers.

For the reviewer (02495033) in South Korea:

Thanks for admitting my manuscript. I'll try my best to avoid the mistakes in detail.