

Dear Manuscript Administration and Journal Staff:

Thank you for checking our manuscript. Our manuscript has been revised according to the feedback. Please see our point-by-point responses below.

On behalf of all co-authors, thank you very much for the comments and suggestions on our manuscript entitled “Bone Morphogenetic Protein-7 Represses Hepatic Stellate Cell Activation and Liver Fibrosis via Regulation of TGF- β /Smad Signaling Pathway” ([*Manuscript ID 47581*](#)). We have carefully studied reviewer’s comments, double-checked our paper and gave the responses point-by-point. Once again, thank you very much for your kind comments and suggestions. If you have any other questions, please feel free to contact me.

Comment 1.

General comment: The manuscript entitled “Bone morphogenetic protein-7 represses hepatic stellate cell activation and liver fibrosis via regulation of TGF β /Smad signaling pathway” investigated a role of BMP7 in liver fibrosis. Although BMP7 has been investigated in liver fibrosis by several groups, this study indicated that high dose of BMP7 at 100ng/ml above can antagonize TGF- β 1 activity in both hepatic stellate cells in vitro and liver fibrosis in vivo. It can also antagonize phosphorylation of Smad3 and p38 in hepatic stellate cells. So their conclusion of BMP-7 role in liver fibrosis is to regulate TGF β /Smad signaling pathway. Specific comments:

1. The main issue of this manuscript from this reviewer is how can they approve that intraperitoneal injection of BMP-7 can reach to the liver. Since model of liver fibrosis is created by injection CCL₄ in peritoneal cavity, a lot of damage was produced and it is difficult for drug to be absorbed into blood.
2. There is a group who used adenovirus to deliver BMP-7 in liver fibrosis model in rat: L Zhong, X Wang, S Wang, L Yang “The anti-fibrotic effect of bone morphogenic protein-7 (BMP-7) on liver fibrosis” International journal of Medical Sciences, 2013. It appears that the authors did not reference this article.

Response 1.

1. It is a reasonable experimental method to perform BMP-7 treatment after successful liver fibrosis modeling. This can be confirmed by not only in the literature recommended by the reviewer(group of late-stage treatment)^[1], but also in other literatures^[2,3].

2. In this paper, we simulate the exploration of therapeutic drugs for hepatic fibrosis and intend to find a molecular targeted drug for the treatment of hepatic fibrosis. Therefore, after the formation of hepatic fibrosis in mice, exogenous BMP7 treatment was given instead of BMP7 prevention.

3. In the article recommended by the reviewer^[1], the authors did not use adenovirus to mediate the expression of BMP7 at all, but directly intraperitoneally injected BMP7.

Comment 2.

The paper is a very interesting, it has a logical aim, results and discussion and it is written in a good language. But I can offer to read it carefully once more and to remove some small typos and mistakes in the text.

Response 2.

We have checked our manuscript very carefully. According to the reviewer's comments, all small typos or mistakes that we can find have been removed, and we have adjusted the format of the manuscript, with highlighted in the revised files.

Reference

- [1] Zhong L , Wang X , Wang S , et al. The Anti-Fibrotic Effect of Bone Morphogenic Protein-7(BMP-7) on Liver Fibrosis[J]. International journal of medical sciences, 2013, 10(4):441-450.
- [2] Zeisberg M , Yang C , Martino M , et al. Fibroblasts Derive from Hepatocytes in Liver Fibrosis via Epithelial to Mesenchymal Transition[J]. Journal of Biological Chemistry, 2007, 282(32):23337-23347.
- [3] Ribera J , Pauta M , Melgar-Lesmes P , et al. A small population of liver endothelial cells undergoes endothelial-to-mesenchymal transition in response to chronic liver injury [J]. American Journal of Physiology - Gastrointestinal and Liver Physiology, 2017,313 (5):G492-G504.

Sincerely yours,

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