

Dear editors,

Thank you all for handling the review of our manuscript, entitled “BRUCE regulation of β -catenin signaling in the progression of drug-induced hepatic fibrosis and carcinogenesis.” We are also grateful for the opportunity to revise this study. Based on your highly constructive comments and suggestions, we have addressed all of your comments and suggestions. These new changes have significantly strengthened this manuscript.

Reviewer Comments:

Referee #1 (Remarks to the Author):

Comments:

The authors of this study investigated the suppressive mechanisms of BRUCE in hepatic fibrosis and HCC development. They reported a chronic fibrosis background induced by hepatic BRUCE KO in mice that recapitulates the fibrosis background in HCC patients, and a BRUCE-dependent suppression of β -catenin activity through the suppression of PKA activity. The subject of this manuscript is of value, but there are a few of defects need to be modified.

1. **Abstract** section-

- a. Should the author change the first word “BRUCE” to: “Baculovirus repeat-containing ubiquitin-conjugating enzyme (BRUCE).” - *Done and thank you.*

2. Should the author briefly describe other factor that can lead to liver fibrosis and HCC in the Discussion section. *Done; please see DISCUSSION for the addition of etiological factors of HVB, HVC, Alcohol and metabolic syndrome to the causes of liver fibrosis and HCC.*

3. The authors described they previously reported the clinical relevance of BRUCE downregulation in a large portion of patients with hepatitis, fibrosis and HCC. Should they give a little more details about the relevance. *-Done; please see DISCUSSION for details.*

4. **Conclusion** section

- a. “We previously reported the clinical relevance of BRUCE downregulation in a large portion of patients with hepatitis, fibrosis and HCC. In addition, BRUCE somatic deleterious mutations or downregulation are found in patients with fibrosis and HCC patients [3].”

- i. It seems that that some of the contents of these two sentences are suspected of repetition (downregulation.....fibrosis and HCC; or downregulation.....fibrosis and HCC). Please check. *-Fixed; please see DISCUSSION for details.*

5. Are there any other mechanisms of hepatic fibrosis and carcinogenesis induced by BRUCE? *-Added additional mechanism of autophagy through which BRUCE could impact hepatic fibrosis and carcinogenesis. Please see DISCUSSION for details.*

Editor's Comments:

Comments:

Issues raised:

1. The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); *- Provided*
2. The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. *- Provided in a PPT file.*
3. PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout. *- revised throughout with both numbers added to the bibliography.*
4. The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text; *- provided.*
5. The reference's number with the square bracket cited in the text should be superscript. *- all in superscript numbers.*