Author's response to reviews

Title: FTY720 Inhibits Proliferation and Epithelial-Mesenchymal Transition (EMT) in Cholangiocarcinoma through Inactivation of STAT3 Signaling

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Author's response to reviews:

Dear editor,

Thank you very much for your reply and help. We acknowledge reviewers’ comments and suggestions for our manuscript “FTY720 Inhibits Proliferation and Epithelial-Mesenchymal Transition (EMT) in Cholangiocarcinoma through Inactivation of STAT3 Signaling” (1860179025133568). The comments from the reviewers are all helpful in revision of our manuscript. We have sent our manuscript to Edanz Company for language editing, and we dealt fully with the criticisms in the revised manuscript, which now is re-submitted. We hope the revised paper would satisfy you and the reviewers.

Response to Reviewers:

First, we’d like to express our appreciation to you for suggesting how to improve our paper. Those comments are all valuable and helpful for revising and improving our manuscript and have made it more publishable.

In the following I specify changes made in the manuscript, replying point-by-point to the reviewers’ comments.

Reviewer #1

1. The issue of activated STAT3 signaling in CC shall be better addressed. Authors shall somehow demonstrate human CC tumors harbor elevated STAT3 signaling by providing immunohistochemical stained tumor slides or by citing published articles revealing the phenomena.

Thank you for your good suggestion. Our previous study "Gankyrin promotes tumor growth and metastasis through activation of IL-6/STAT3 signaling in

2. Only one cell line for respective animal study seemed to be short. HuCCT1 was for in vivo invasion/metastasis assay while QBC939 was for tumor growth study in xenograft mice.

Thank you for your suggestion. We performed animal study using other CC cell lines. The data was shown in Fig. S1 and Fig. S2.

3. If any published reports have reported Stat3 inhibitors could render similar tumor suppressive effect on CC as FTY720 did, these pertinent articles shall be discussed.

We have cited the pertinent articles about STAT3 inhibitors and discussed the tumor suppressive effect of STAT3 inhibitors in discussion section.

4. The statement of “without notable “Side Effect” shown in line 23 of page 10 needs some experimental data. Are there any evidence to support the statement? Shall control mice lacking tumor be treated similarly and then followed by close assessment for evaluating the drug’s side-effect on healthy mice?

Thank you for your good suggestion. We have shown the data for evaluating the drug's side-effect in Figure S3.

5. Discussion section virtually reiterated what have been described in the result section which made the article reads redundantly. Citing additional publications in the discussion section for comparing data generated from various groups would improve the quality of the manuscript.

Thank you for your suggestion. We have edited the discussion section and cited additional publications in the discussion section as your suggestion.

6. English writing could be better improved. For example, line 29 of page 8 stated:

And, FTY720 treatment also strongly decreased.

It is an uncommon writing grammatically.

The manuscript has been thoroughly checked by Edanz Company (www.edanzediting.com/bmc1) and the editing and grammatical mistakes have been corrected carefully.

7. Some statements could be added with clarity. For example: The IHC analysis showed the changes of Ki-67,cleaved-caspase-3 and CD31 in different group (Fig. 6C), can be added with a few extra words “respectively assess tumors' ability of proliferation, apoptosis, and forming microvessels”.

Thank you for your suggestion. We have thoroughly checked the paper and corrected the mistakes as your suggestion.
Reviewer #2
- Page 3, line 9, change “But” to “However,”.
- Page 8, line 28, delete “a”; line 29, change “And” to “In addition”.
- Page 10, line 10, change “group” to “groups”; line 11, add “were” after “which”.
- Page 11, line 1, change “and halting” to “to halt”.
- Page 12, line 3, “p-STST3” should be “p-STAT3”.

Thank you for your kindly suggestion for language editing of our paper. We have thoroughly checked the paper and corrected the mistakes as your suggestion.

Yours sincerely

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