

List of Responses

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "RON in hepatobiliary and pancreatic cancers: Pathogenesis and potential therapeutic targets" those comments are all valuable and helpful for revising and improving our paper. We have studied comments carefully and have made correction which we hope to meet with approval. Revised portion are marked in yellow in the paper. The main corrections in the paper and the responds to the reviewers' comments are as follows:

Reviewer #1:

1. This review manuscript describes roles of RON in carcinogenesis and its application as a drug target of hepatobiliary and pancreatic cancers. In my opinion, the way of presentation is not attractive enough. Authors should add value to their paper through graphic, pictures, diagram and so on. I believe that if authors reduce molecular info and add more relating clinical info. It will probably help this point.

Response: Thank you for your suggestions. We have added more details in Figure 1 and Table 1 which are all highlighted in yellow. We added more information of the RON downstream signaling pathways in Figure 1. Moreover, we added more details of In vitro effects, effects in animal tumor

models, as well as clinical trial information in Table 1. We believe that it will make the presentation more attractive.

2. Keywords: No space between " Key words". Please delete "Protein-" from this session and add "hepatobiliary" as additional keyword.

Response: Thanks for your careful checks. We have change "Key words" to "Keywords" in page 3 line 22 and marked in yellow. We have deleted "Protein-" and add "hepatobiliary" as additional keyword as you suggested, which are all highlighted in yellow too.

3. Change the heading "THE CANCER PATHOGENIC ROLE OF RON AND c-MET" to "Roles of RON and c-MET in Carcinogenesis".

Response: Thanks for your reminding. In response to your suggestion, we have modified the "THE CANCER PATHOGENIC ROLE OF RON AND c-MET" into "Roles of RON and c-MET in Carcinogenesis" in page 6 line 2.

4. In many places, authors used evidence in singular form but it should be plural form in the content.

Response: Thanks for your careful checks. We have changed every “evidence” in plural form in page 5 line 25, in page 6 line 18, in page 10 line 8, in page 13 line 22, in page 16 line 16, which are all marked in yellow.

5. Authors should add more illustrations, diagrams, pictures, etc. It will help audience to understand easily and attract to them

Response: Thanks for your comments. We have added more information in Figure 1 and Table 1, which we believe will help this point.

6. Please use "hepatocellular carcinoma" or "hepatoma" (both are malignant tumor) instead of hepatocarcinoma

Response: Thanks for your comment. We have change "hepatocarcinoma" into " hepatocellular carcinoma " in page 3 line 22.

7. Please rewrite for more comprehensive and easier to follow

Response: Thanks for your comments. We have modified the manuscript by the suggestions from all the reviewers. Moreover, we have added more information in Figure 1 and Table 1. All the changes have been marked in yellow. We believe that all these changes will make this minireview more comprehensive and easier to follow.

Reviewer #2:

Thanks for the opportunity to review the manuscript entitled "RON in hepatobiliary and pancreatic cancers: Pathogenesis and potential therapeutic targets". The manuscript is well written and in a very important topic due to the poor prognosis and lack of targeted therapies in hepatobiliary and

pancreatic cancers. However, there are minor comments that needed to be addressed before publication:

1. Please correct some typos throughout the manuscript.

Response: We feel great thanks for your professional review work on our article, which are all valuable and helpful for revising and improving our paper. We have corrected all the typos as you marked in our review and we have highlighted them in yellow.

2. In the introduction section, please clarify the sentence: “which are connected via to...”

Response: Thanks for your careful checks. We have justified the original sentence “The RON receptor is initially synthesized as a biologically inactive single-chain precursor (pro-RON), then cleaved into a 145 kDa beta chain and a 35 kDa extracellular alpha chain, which are connected to form the mature receptor via a disulfide bond. ” into “The RON receptor is initially synthesized as a biologically inactive single-chain precursor (pro-RON), then cleaved into a 145 kDa beta chain and a 35 kDa extracellular alpha chain, which are linked by a disulfide bond, forming the mature receptor.” We believe that it is easier for readers to understand.

3. Why did you decide to include c-MET in the chapter “The cancer pathogenic role of RON and c-MET”? The next chapter is only focused on

RON.

Response: Thanks for your comments. Firstly, RON and c-MET belongs to the same family. We believe that the induction of the role of c-MET in carcinogenesis will make readers easier to further understand RON activation and signaling pathway mechanisms. Secondly, we not only shared the recent updates of tyrosine kinase inhibitors and antibody drug conjugates specific to RON but also c-MET in table 1. So, we believe that this part is necessary in this review.

4. Please revise the order of the chapter “Aberrant RON signaling and expression in cancer pathogenesis”: cell line studies should appear first and human tumor samples next.

Response: Thanks for your comments. In this chapter, the order is based on different cancer types but not cell line studies and human tumor samples. We firstly write the relationships between breast cancer and dysregulated RON signaling and expression. Then, we write the relationships in other tumors such as hepatocellular carcinoma.

5. In the same chapter, and also in the next one, there are so many sentences without reference. Please add the appropriate references.

Response: Thanks for your careful checks. We have added appropriate reference after the sentences as you suggested. All this added reference is

marked in yellow.

6. Abstract too long and repetitive --> please revise

Response: Thanks for your careful checks. We have revised the abstract.

Editor Comments

(1) Science Editor: 1 Scientific quality: The manuscript describes a review of the RON in hepatobiliary and pancreatic cancers. The topic is within the scope of the WJG. (1) Classification: Grade B and Grade C;

(2) Summary of the Peer-Review Report: The manuscript is well written and in a very important topic. However, the way of presentation is not attractive enough, the authors should add value to their paper through graphic, pictures, diagram and so on. The questions raised by the reviewers should be answered; and

(3) Format: There is 1 table and 1 figure. A total of 90 references are cited, including 13 references published in the last 3 years. There are 12 self-citations, which are related to this paper. 2 Language evaluation: Classification: Grade B and Grade B. A language editing certificate issued by ELIXIGEN was provided.

3 Academic norms and rules: No academic misconduct was found in the Bing search.

4 Supplementary comments: This is an invited manuscript. The study was

supported by 3 grants. The topic has not previously been published in the WJG.

5 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); and (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.

6 Re-Review: Required.

7 Recommendation: Conditional acceptance.

(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);

Response: we are very sorry for did not provide the approved grant application form(s). We have upload corresponding document in the attachment.

(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.

Response: we are very sorry for missing this part, we have provided a PowerPoint including the original figure in the attachment.