May 17, 2021

Dr. Lian-Sheng Ma
Editor-in-Chief
World Journal of Gastrointestinal Oncology

Dear Dr. Lian-Sheng Ma:

Thank you very much for your letter dated May 8. 2021, regarding our manuscript "Involvement of integrin-activating peptides derived from tenascin-C in colon cancer progression" (Manuscript NO: 64614), together with the comments from two reviewers.

The comments from the reviewers were highly insightful. We have revised the manuscript in accordance with the reviewer's comments. Appended to this letter is our response to each of the reviewer's comments.

We believe that the manuscript has been improved satisfactorily and hope it will be accepted for publication.

Yours sincerely,

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Reviewer #1:

Thank you very much for your valuable comments. Our responses are as follows.

1. Although this article mainly deals with the role of TNC in malignancy, it has also been shown to be important in both acute and chronic inflammation + fibrogenesis and tissue remodelling. Indeed the authors have touched upon this. However, I suggest adding a small section separately on chronic inflammation before the section that deals with cancer. To accommodate this, the introduction can be shortened if necessary. The chronic inflammation leading to carcinogenesis becomes more evident if this is done.

Our response: In accordance with the comment, we have added descriptions regarding TNC-related chronic inflammation to the revised manuscript (lines 81-91, 160-162).

2. In the CAC section, the authors mention ATN-161, a peptidic antagonist of integrin α5β1 and αvβ3. In this experimental model, was it known through which sub-unit the anti-cancer properties were exerted? If known please mention including if there are any pre-clinical models in progress.

Our response: In analysis using AOM/DSS model (Inflamm Bowel Dis. 2019;25(4):732-741.), the authors mentioned that ATN-161 inhibits CAC development via inhibition of integrin alphavbeta3-mediated angiogenesis. However, no recent development status of ATN-161 has been available. These descriptions have been added in the revised manuscript (lines 382-390).

3. Indeed the authors end with a note mentioning the potential for therapeutic targeting, which is encouraging. If any models are known that are in progress which take us closer to translation of these targets, it would be useful to mention here.

Our response: While no recent development of ATN-161 has been reported, OS2966, a humanized monoclonal antibody targeting human beta1-integrins, is in Phase I clinical trial for the treatment with recurrent/progressive glioma (*Pharmaceutics* 2021, 13(1), 40). In addition, peptide FNIII14 is in preclinical studies for treatment of several malignancies. Application of these agents would also become promising strategies for treatment of colon cancer. These descriptions have been added in the revised manuscript (lines 405-413).

In addition, we have rewritten the descriptions in the previous manuscript for improved readability.

Changes and corrections of descriptions are indicated by red font in the revised manuscript.

Reviewer #2:

Thank you very much for your valuable comments. Our responses are as follows.

• There was a problem with the word file, all the symbols were not apparent on the word file as (α-β- etc)

Our response: We have modified the descriptions of all the symbols in the revised manuscript (e.g., α->>alpha-).

• Introduction on colon cancer line 304-308 lacks references. Also introduction to the colon cancer needs further detail on the prevalence and current problem of the current therapeutic biological therapy, to be presented in more details.

Our response: In accordance with the comment, we have added the references and the introduction in more details to the revised manuscript (lines 167-182).

• Please change therapy resistance to>> therapeutic resistance or resistance to therapy in line 179

Our response: We have changed the descriptions in the revised manuscript (lines 304).

• Show >>showing in line 135.

Our response: We have changed the descriptions in the revised manuscript (line 137).

• The authors should start with colon cancer and then as subcategory CAC.

Our response: In accordance with the comment, we have changed the order of the sections in the revised manuscript. Along with these changes, we also modified the related descriptions in the revised manuscript (lines 234-243, 365-368)

• note: Figure 1 is very similar to your previously published figure, only the spaces were removed(modified from ref 62), also in that previous paper they stated the same theory in details.

Our response: We have modified the descriptions of Figure 1 for readability of mode of action in the revised manuscript. With these revisions, the differences between this review and our previously published figure are more obvious.

In addition, we have rewritten the descriptions in the previous manuscript for improved readability.

Changes and corrections of descriptions are indicated by red font in the revised manuscript.