

ANSWERING REVIEWERS



January, 11, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6157-review_revised.doc).

Title: Title: Role of the Tissue Microenvironment as a Therapeutic Target in Hepatocellular Carcinoma

Author: Bhavna Rani, Yuan Cao, Andrea Malfettone, Ciprian Tomuleasa, Isabel Fabregat, Gianluigi Giannelli

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6157

The manuscript has been improved according to the reviewers' suggestions:

1 The format has been updated

2 Revision has been made according to the suggestions of reviewer # 00069464

RE: "It would be much better if the authors can add critical opinion about how possibly these compartment can be used as target."

AU: We have briefly discussed this point in the "Conclusion" paragraph. However, the review was commissioned to be focused on the tissue microenvironment (as in the original letter from WJG) and not on therapeutic aspects.

RE: Please modify the title to cover all the content of the manuscript.

AU: We have already modified the title according to the request by a previous reviewer.

RE: The reference should be updated.

AU: References have been updated.

2 Revision has been made according to the suggestions of reviewer # 00053560

1. As discussed for the previous reviewer, this review cannot take into consideration all the aspects of HCC including etiologies, but just few aspects mainly focused on the tissue microenvironment.
2. We respect the reviewer's opinion but respectfully disagree. Five other reviewers did not express the same opinion.
3. We do not believe that the introduction should be a focused paragraph, otherwise it would not be an introduction. The abstract, in few words, simply describes the topic of the review.
4. This point seems somewhat contradictory. Previously, the same reviewer is not satisfied by the discussion of TGF in HCC, now s/he doesn't like the discussion of TGF in other tumors. We believe that it is important to discuss, albeit briefly, the role of TGF also in other malignancies.
5. Again, this review is focused on TGF-beta and Ln-5 in HCC. Thus, it makes sense to discuss TGF-beta with respect to CAF. Also in this case the reviewer seems to adopt a rather harsh critical approach rather than making a constructive reading of the manuscript.
6. In our opinion the review is already quite long, so we have to be less detailed in some points. Also in this case we have the impression that the reviewer is not being fair.
7. This reviewer might read reference number 63 by Knipe L. et al, that we have referred to. In

that paper the point is clearly explained. We are not sure if the reviewer is aware of such organelles secreting TPA. As regards the role of the non-Smad pathway, we have discussed this point.

8. We have amended this point.
9. We have added some discussion in this regard.
10. The manuscript has been checked by a professional text reviser and native English speaker, who was unable to find a single grammar/spelling/expression error; by contrast, she found so many in the reviewer's comments as to make them practically incomprehensible (just one example: "*the descriptions does not look those focus on..*"). In her humble opinion this reviewer should be kindly asked to refrain from making comments on language quality because s/he is clearly unqualified to do so.

Revision has been made according to the suggestions of reviewer # **02526292**

- 1) The reviewer is right, TGF-beta is only part of the microenvironment components. I am not sure which title the reviewer has read, but in the current version TGF-beta is not mentioned in the title, and consistently, it is not mentioned in the abstract.
- 2) Also in this case I am afraid that the reviewer must have revised the first version and not the second. In this manuscript there are a total of 106 references.
- 3) Figures were referred in the text (see CAF and Cancer Stem Cell paragraphs). Probably, as suggested above, the version of the manuscript he revised was not the right one.
- 4) The reviewer is right. We have amended all the points:
 - i) The sentence has been moved to a different place in the Introduction; ii) the TNF acronym has been used only once; iii) the acronym has been used only referred to "side population cells". The "label retaining liver cells" concept has been omitted as suggested.

3 References and typesetting have been corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Prof. Gianluigi Giannelli, MD
Department of Emergency and Organ Transplantation
University of Bari, School of Medicine
Bari, Italy