

## ANSWERING REVIEWERS



June 19, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 10537-review.docx).

**Title:** Cancer-associated fibroblasts in digestive tumors

**Author:** Lei Huang, A-Man Xu, Sha Liu, Wei Liu, Tuan-Jie Li

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 10537

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

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers

(1) Reply to Reviewer #00292853:

a) *This review would markedly benefit from the incorporation of tables and figures. For example, a figure with a typical histology showing both tumor cells and CAFs could be shown; and a figure showing the interplay between CAFs with tumor cells and some of the major molecules involved in this interaction that are mentioned throughout the text could be shown. In addition, the origin of those molecules either derived from tumor cells or CAFs can be illustrated. A figure showing CAFs and their different roles in EMT, prognosis, chemoresistance, immunity, progression, therapy etc. with some of the molecules involved could be designed.*

Sincerest thanks for the thoughtful and constructive suggestions. As pointed out by the reviewer, such incorporation would greatly improve our review, and we have added the corresponding figures and tables where appropriate as suggested.

b) *Unfortunately, a last paragraph entitled like "Conclusions and future work" or something like that is missing. Such an outlook is needed.*

Sincerest thanks for the thoughtful and constructive suggestion. We have added a novel section entitled "Conclusions and outlook" at the end of the main text as proposed.

c) *There is evidence that the intra-tumor stroma percentage in cancers can serve as prognostic marker, (e.g. A. Huijbers, R.A. Tollenaar, G.W. v Pelt, E.C. Zeestraten, S. Dutton, C.C. McConkey et al. The proportion of tumor-stroma as a strong prognosticator for stage II and III colon cancer patients: validation in the VICTOR trial. *Ann Oncol*, 24 (2013), pp. 179-185.) This should be incorporated into the respective section on CAFs and prognosis.*

We thank the reviewer very much for the thoughtful and constructive suggestions. As pointed out by the reviewer, it has been revealed that the intra-tumor stroma percentage can serve as a prognosticator as mentioned in the literature mentioned, and we have added this important viewpoint and cited the corresponding paper in the "CAF's and prognosis" part of our manuscript.

d) p.8: *the correct name of the first author of ref. 42 is Olumi.*

We thank the reviewer very much for the important reminder. We have corrected the name accordingly.

e) *The authors should add a few sentences about differences/similarities of CAFs in primary tumors versus CAFs in the corresponding metastases. Are there differences?*

We thank the reviewer very much for the thoughtful and constructive suggestion. The reviewer does have raised an interesting and important issue concerning differences/similarities of CAFs in local versus distant ecosystems. To our knowledge and after a thorough and careful literature retrieval, we find that the corresponding data are not abundant, however. We have added a novel section named “CAF<sub>s</sub> in primary tumors versus in metastases” describing what we know and have found about the issue in our manuscript as proposed.

(2) Reply to Reviewer #02446368:

*This is an interesting paper.*

Sincerest thanks for the reviewer’s positive, supportive and constructive comment.

(3) Reply to Reviewer #01333103:

a) *This review reported a broad explanation of CAFs and their role in tumor microenvironment. The review is well written and highlights a topic of great scientific interest I suggest some minor modifications. 1. The title is perhaps not appropriate because the manuscript is not only about the role of CAFs in digestive tumors, but also in other tumors. Otherwise, we recommend to improve the review with a final paragraph specifically devoted to underline the role of CAFs in digestive tumors only*

Sincerest thanks for the reviewer’s positive and supportive attitude towards our manuscript, and the constructive and thoughtful comment and recommendation. We have added a novel paragraph named “Conclusions and outlook” at the end of the main text as suggested, concluding and highlighting the roles of CAFs in digestive tumors.

b) 3. *In the paragraph CAFs and EMT, it is necessary to better explain the role of CAFs in EMT process using more recent reports (i.e..Yu Y, Xiao CH et al. Br J Cancer. 2014 Feb 4;110(3):724-32)*

We thank the reviewer very much for the constructive and thoughtful suggestion. We have added the corresponding recent reports concerning the role of CAFs in EMT process in the “CAF<sub>s</sub> and tumor EMT” section as suggested.

c) 4. *More generally, we recommend to review the bibliography using more updated references.*

Sincerest thanks for the reviewer’s thoughtful suggestion. We have added the novel references accordingly, and updated the bibliography as suggested.

d) 5. *Errors have been detected in some of the abbreviations (i.e.the double allocation for LPA abbreviation: at page 6 the authors indicate LPA as abbreviation of the lysophosphatidic acid and subsequently at page 7 as abbreviation of lysophosphatidic acid). HGF is present only as abbreviation*

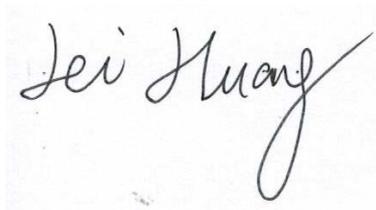
We thank the reviewer very much for the thoughtful and constructive suggestion. According to the

original article, LPA is short for lysophosphatidic acid, (Mazzocca A, Dituri F, Lupo L, Quaranta M, Antonaci S, Giannelli G. Tumor-secreted lysophosphatidic acid accelerates hepatocellular carcinoma progression by promoting differentiation of peritumoral fibroblasts in myofibroblasts. *Hepatology* 2011; 54: 920-930 [DOI: 10.1002/hep.24485]), and we have made the corresponding changes accordingly. HGF is short for hepatocyte growth factor, and we have added the full name where appropriate.

3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in black ink that reads "Lei Huang". The signature is written in a cursive style with a long, sweeping tail on the letter "g".

Lei Huang, MD  
Department of Gastrointestinal Surgery  
the First Affiliated Hospital of Anhui Medical University  
No. 218, Jixi Road, Hefei, Anhui Province  
230022-China  
Fax:+86-551-63633742  
E-mail: huangleizhenting@126.com