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April 22, 2016

Dr. Ze-Mao Gong
Science Editor, Editorial Office
World Journal of Gastroenterology
Baishideng Publishing Group Inc.

Dear Dr. Gong

Re: Manuscript No. 25619 "Fibroblasts, an inconspicuous but essential player in colon cancer development and progression"

We express our sincere gratitude to your invaluable comments on our above mentioned manuscript. We read the comments thoroughly and revised the manuscript in response to the comments as follows. In the revised manuscript, we indicate the major modified points in red.

Reviewer #1 (code number 0050552)
The authors reviewed the role of cancer-associated fibroblasts (CAFs) in cancer initiation and progression. They suggested that targeting CAFs can be a novel strategy to treat cancer. This paper is an important contribution and I recommend that it be accepted for publication.

We appreciate the reviewer's thoughtful comments and modified the manuscript to increase its readability.

Reviwer #2 (code number 00560095)
#1. The reviewer recommended us to focus on CAFs in colon cancer as follows.
"Although the focus is on colon cancer, the authors choose to discuss also finding in other tumor types, which is valuable, but also decreases the depth of the review. An example of that would be that a complete review could be written on the origin on CAFs, but summarizing the origin of CAFs in 2 pages for multiple tumor types seems somewhat difficult, without losing important information. I noticed that sometimes studies with contradictory findings do not get equal attention (like for the role of EMT). I would recommend to have a bit more balanced overview of the role of CAFs in CRC. This would mean somewhat less attention to other tumor types and/or the specific role of the immune regulation."
In response to this recommendation, at the end of the introduction section, we described as follows.
"We will herein discuss the pathophysiological roles of CAFs and their clinical relevance mainly in colorectal cancer (CRC), but will mention CAFs in other types of cancer if necessary."
Moreover, in the second paragraph of page 7, we described as follows, to stress that the main source can be resident fibroblasts.
"The most possible cellular source of CAFs in CRC is resident fibroblasts in colon tissues."
Furthermore, at the beginning of the second paragraph of page 8, we also described as follows, to remind the readers that we will mention the observations obtained from other types of cancers.
"Other types of cells are proposed to be a cellular source of CAFs, based on the analyses on other conditions than CRC."

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#2. The reviewer recommended us to discuss crosstalk between fibroblasts and epithelial cancer cells, by citing papers as follows. “Several important papers are missing in this regard, for example Berdiel-Acer et al, Mol Oncol. 2014 Oct;8(7):1290-305, Calon et al Semin Cancer Biol. 2014 Apr;25:15-22 and more recently Vellinga et al Oncogene. 2016 Mar 21. doi: 10.1038/onc.2016.60, but also several other in relation to cross talk between fibroblasts and epithelial cancer cells and the prognostic relevance of SMA+CAFs in CRC.”
We agreed with the recommendation. Thus, we discussed the observations described by Berdiel-Acer in the fourth paragraph of page 11. Moreover, we mentioned the observations reported by Vellinga in the third paragraph of page 12.Finally, we described the findings by Calon’s group by citing their original paper published in Cancer Cell, in the second paragraph of page 13. We hope that the discussion on these papers will greatly help the readers understand the cross-talk between fibroblasts and epithelial cancer cells and its roles in tumor progression and metastasis.

#3. The reviewer recommended us to reorganize the Future Perspective section as follows.
“The future perspective contains a lot of data which would fit better in earlier parts of the manuscript.”
We agreed with the recommendation, we moved the paragraph describing CAF markers to the beginning of the Section concerning the origin of CAFs (the third paragraph of page 6).

The reviewer further raised the possibility that SMA expression is restricted to fibroblasts in culture. We agreed with this point-out and described as follows in the third paragraph of page 6.
“α-SMA, a robust CAF marker, is also expressed by normal colonic fibroblasts under in vitro culture conditions.”

#4. In response to the recommendation to provide the text to the figures, we added the text to explain the contents of each figure.
Moreover, we more precisely explain what each symbol indicates in Table.

We believe that we have responded to the comments fully and hope that the paper is now acceptable for the publication in World Journal of Gastroenterology.

Yours sincerely,

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