Verona, 07/13/2018

ANSWERING REVIEWERS

Name of the journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 40058

TITLE: The histo-molecular oncogenesis of pancreatic cancer: from precancerous lesions to invasive ductal adenocarcinoma

Dear Editors and Reviewer, *World Journal of Gastrointestinal Oncology*

First of all, we want to thank all of you for your important comments and suggestions, as well as for the words of praise about our paper, and to give us the possibility to send a revised version of our manuscript. Here we answer point by point to all your evaluable questions.

Reviewer 1.

Q1. The authors described fragmentary information on precursor lesions of pancreatic ductal cancer (PDAC) without providing their hypothesis on the mechanisms underlying the progression of precursor lesions to PDAC. The authors should discuss their hypothesis on the pathway from precursor lesions to PDAC at molecular and cellular levels.

Answer. Thanks for this observation. We have added a sentence at the end of the Introduction section indicating that through a multi-step carcinogenesis, with the accumulation of cellular and molecular alterations, each of the PDAC precursor may lead to the development of invasive ductal adenocarcinoma. We have described in the manuscript all the most important aspects about the different PDAC carcinogenetic hypothesis/evidences, as also indicating by the other reviewers.

Q2. The authors described morphological changes observed in each precursor lesion but their explanation on the figures were vague and is hard for non-pathologists to understand precisely the characteristics of the lesions. The authors should indicate morphological changes in the figures by using arrows, arrowheads, and so on.

Answer. Thanks a lot for your comment. Following your valuable suggestions, we have added to the figures more arrows and arrowheads as requested, and also asterisks.

Q3. The authors should describe the molecular profiles not in a systematic manner. The authors should discuss how each molecular change can contribute to PDAC development. The last section on the recent advances and future perspective should be incorporated into the preceding sections.

Answer. We have followed the guidelines for reviews and not for systematic reviews. We agree with the reviewer when he/she indicated that the description of PDAC precursors "should be performed not in a systematic manner". Indeed, we have decided to present every PDAC precursor step-by-step, but maintaining separated the last section on recent advances and future perspectives will guarantee that the data are not presented in a systematic manner. For these reasons, we have followed the first suggestion of this Reviewer, but at the same time we cannot follow the last suggestion of this same Reviewer in the last part of Q3: we thank this Reviewer for the valuable comments.

Q4. The manuscript contains innumerable errors in syntax and therefore, should be extensively edited by a professional editor proficient in writing scientific English.

Answer. The manuscript has been corrected by Dr. Lawlor, English mother-tongue. The other reviewers have indicated "minor language polishing", and we have further improved the English language in this revised version of the manuscript following the specific instructions provided by the other Reviewers.

Reviewer 2.

Q1. This manuscript reviewed some aspects of precursors of PDAC, including clinical features, histological and molecular characters of IPMN, PanIN, ITPN and MCN. Recent advances and future research direction in this field were also presented in this manuscript. Early detection of PDAC is the most important factor affecting the prognosis of patients with PDAC. It is necessary to understand and recognize typical precursors of PDAC for early diagnosis of PDAC. This manuscript provided valuable information about the profiles of these diseases and showed future perspectives on this topic. The content of this manuscript may help physicians comprehend the features and differentiation of MCN, IPMN, PanIN and ITPN. This may play a role in promoting early detection rate of PDAC in clinical practice.

Answer. Thanks a lot for your revision and for considering as acceptable our paper in its original version. Your words of praise have been much appreciated. We totally agree with your opinion: comprehending the role of PDAC precursor lesions in PDAC carcinogenesis may play a role in promoting early detection rate of PDAC in clinical practice.

Reviewer 3.

Q1. The current review not only summarized the clinical feature, histopathological characteristic and the molecular profile of the PDAC precursor lesions, but also highlighted the recent advances

and future perspectives on PDAC carcinogenesis, which is of great importance for the comprehension of PDAC carcinogenesis as well as the design of early detection techniques and more effective therapeutic strategies. Except for some grammatical and spelling errors to be corrected, this review is a truly excellent work. And I think the authors should carefully revise the highlighted parts in the attached file before acceptance.

Answer. Thanks a lot for your revision and for considering our paper truly excellent work. Your words of praise have been much appreciated. Thanks also for having highlighted some specific parts in the text for the revision of the English language. We have carefully revised all these parts, highlighting our changes.

Reviewer 4.

Q1. It would be better if the authors list a table to compare the features of these four PDAC precursor lesions. Some minor English language mistakes should be corrected.

Answer. After having corrected minor English mistakes, we have also prepared a new table, named Table 2, as suggested by this Reviewer, for comparing the features of PDAC precursor lesions.

Concluding, we want to thank the Editors and the Reviewers for the possibility to send a revised version of our manuscript. Thanks to the important suggestions received, we hope that now the manuscript has been improved and also acceptable for publication on World Journal of Gastrointestinal Oncology.

The only request we have is to consider this manuscript as a Review (as originally invited – topical review) and not as a mini-review "only". We think that if this paper will be published as a mini-review, the term "mini-review" does not represent the real in-depth analysis of the argument that this manuscript is presenting (many pages, 76 references, 6 figures, 2 tables); we think that this paper should be named as "Review", but this is a request only, and we will respect the decision of the Editor on this point, which is of importance for us.

Thank you.

Yours sincerely,

The corresponding author:

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