Dear editor,

Thank you very much for your email and a chance to revise our manuscript (manuscript ID: 81757). We now resubmit the revision of our manuscript. We appreciate editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript. We tried our best to improve the manuscript and made some changes in the manuscript.

Thank you again for your time and kind help.

Yours sincerely,

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Our point-by-point responses to editor and reviewers' comments are

as the following.

Editor Comments:

I have reviewed the Peer-Review Report and the full text of the manuscript, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

1. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript

Response: Thank you for your advice. We have made the appropriate modifications.

2. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision.

Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Response: Greatly appreciate your suggestion. We used the RCA database, which is a useful database

3. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Response: Thank you for your reminder, we have done as requested.

Reviewer Comments:

Reviewer 1:

1) The rationale of why the authors came up with this research is scanty and is related to a lack of novelty: please highlight what this manuscript might add

Response: Thank you for your suggestion. We believe that pancreatic cancer is a highly malignant tumor with a poor prognosis. Moreover, the current studies on pancreatic cancer have ignored the role of the intratumor microbiome. Although a lot of progress has been made in the study of tumor microbiome related to pancreatic cancer, there are still

many unanswered questions. Therefore, we reviewed the cutting-edge progress of tumor microbiome in pancreatic cancer to provide some ideas for future research. So we revised parts of the Core tip and introduction section.

2) What is the information that is not exactly available that motivated the authors to come up with this information. What are the current caveats and how do the authors highlight the current research in answering them? If not they need to address in background and in future directions

Response: Greatly appreciate your suggestion. We have added this in the introduction and conclusion section.

3)State of the art figures are required: scale bar should be provided in high resolution.

Response: Thank you for your reminder, we have done as requested.

4)The authors could provide a little more consideration of genomic directed stratifications in clinical trial design and enrolments.

Response: Thank you for your reminder. The current status of studies on genomic alterations and intratumor microbiome is insufficient, so the

inclusion of genomic directed stratifications is difficult. Therefore, we added this aspect of the study as a deficiency in the concluding section.

5)The underlying message here is that more precision and individualized approaches need to be tested in well-designed clinical trials – a challenge, but I would be interested in their perspective of how this might be done. If beyond the scope of the manuscript, this should be highlighted as a limitation

Response: Greatly appreciate your suggestion. But as we all know, individualized and precise treatment for pancreatic cancer patients is a current research priority. As the reviewer say, this is beyond the scope of this review. We cover this limitation in the concluding section.

6) The authors need to highlight what new information the review is providing to enhance the research in progress

Response: Greatly appreciate your suggestion. We have added this in the conclusion section.

7) This reviewer personally misses some insights in the introduction/discussion regarding genetic alterations and the potential relationship between those and the microbiome/immune landscape of PDAC. Indeed, especially the K-Ras mutation, carry the heaviest burden in the progression of pancreatic precursor lesions

into pancreatic ductal adenocarcinoma (PDAC). The tumor microenvironment is one of the challenges that hinder the therapeutic approaches from functioning sufficiently and leads to the immune evasion of pancreatic malignant cells. Mastering the mechanisms of these two hallmarks of PDAC can help us in dealing with the obstacles in the way of treatment. In this review, we have analyzed the signaling pathways involved in PDAC development and the immune system's role in pancreatic cancer and immune checkpoint inhibition as next-generation therapeutic strategy. The direct targeting of the involved signaling molecules and the immune checkpoint molecules, along with a combination with conventional therapies, have reached the most promising results in pancreatic cancer treatment (please refer to PMID: 33918146 and expand)

Response: Thank you for your reminder. We agree that KRAS mutations are critical in the progression of pancreatic cancer. The current study on the mechanism of intratumor microbiome and KRAS mutation in pancreatic cancer is only shown in the study of Alam et. al. (PMID: 35120601). We have added this to the conclusion.

Reviewer 2:

The association with viruses needs to be added. For example, some reports support or deny the association between HBV and HCV and pancreatic cancer carcinogenicity. These reports should also be

summarized. A review of bacterial-viral interactions for the development and carcinogenesis of virus-associated cancers is also needed.

Response: Greatly appreciate your suggestion. At this stage, studies on the intratumor microbiome are mainly focused on bacteria and fungi, and the mechanisms related to viruses and pancreatic cancer are not sufficiently studied. Therefore, we added this section in the conclusion as a shortcoming and a direction for future research.