Dear Editor and dear reviewers,

Thank you for your letter and the reviewers' comments concerning our manuscript entitled "Research on INPP4B in digestive system tumors" (NO. 86360). Those comments are valuable and very helpful. We have read through comments carefully and have made corrections. Based on the instructions provided in your letter, we uploaded the file of the revised manuscript. Revisions in the text are shown using red highlight for additions, and strikethrough font for deletions. The responses to the reviewer's comments are marked in red and presented following.

Reviewer #1: The title may be revised to be more specific. In Table 1, the name of column "mechanism" is not clear enough, does it mean "target" or some other molecular pathway? The concrete function of PI(3)P on SGK3 activation may be added in Figure 2.

Response: We are grateful for the suggestion. We have revised the manuscript accordingly. Our point-by-point responses are detailed below.

Firstly, Thank you for your suggestion. As suggested by reviewer, we revised our title from "Research on INPP4B in digestive system tumors" to "The role of inositol polyphosphate-4-phosphatase type II in the oncogenesis of digestive system tumors" on page 1 to make it more detailed.

Secondly, We agree with the comment and re-wrote the word "mechanism" in the revised manuscript as the following: "Molecular pathway" in Table 1.

Finally, We are grateful for the suggestion. As suggested by the reviewer, we have added more details in Figure 2 and on page 12. We marked the blue arrow for activate. PI (3) P, produced by INPP4B, can bind to SKG3 to activate it, which promotes the occurrence and development of tumors and resists the process of apoptosis of tumor cells. Mechanistically, INPP4B overexpression enhanced the phosphorylation of SGK3 (p-SGK3) in cancer cells, whereas INPP4B knockdown enhanced the the phosphorylation of AKT (p-AKT) level in cancer cells.

Reviewer #2: This is a good general summary of the topic. INPP4B cannot both be a proto oncogene and a tumour suppressor gene so the writers have recognised the fact we still have a lot of understanding of the INPP4B pathways of carcinogenesis.

Response: Thank you for your summary. We really appreciate your efforts in reviewing our manuscript. To be more clearly and in accordance with the reviewer concerns, we have added a more detailed interpretation using red highlight. The abnormal expression of INPP4B plays an important role in the development of digestive system tumors. Studies on INPP4B provide new molecular insights for the diagnosis, treatment and prognosis evaluation of digestive system tumors.

Science editor: The manuscript has been peer-reviewed, and it' s ready for the first decision. Language Quality: Grade B (Minor language polishing) Scientific Quality: Grade C (Good)

Response: Thank you for your careful review and advise. We have sent our revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When we submitted the subsequent polished manuscript, they have provided the new language certificate along with the manuscript.

Company editor-in-chief: 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. The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English

language editing company. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240. 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. 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/. Uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". 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) 2023.

Response: We are very grateful to your comments for the manuscript. According to your advice, we amended the relevant part in manuscript. All of your questions were answered one by one.

Firstly, We have sent our revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When we submitted the subsequent polished manuscript, they have provided the new language certificate along with the manuscript.

Secondly, we used RCA database for more information and searched "INPP4B" and "tumor" again in PubMed and in the CNKI series full text database retrieval system from 2000-01 to 2023-8. We included more 7 papers in our passage. There were more evidences on page 10-12 and in Table 1 to support decreased INPP4B expression activates the phosphorylation of AKT, which leads to the occurrence and development of gastric cancer. However, a new study on page 12 and in Table 1 showed the roles of INPP4B in the prognosis of gastric cancer patients might be paradoxical. In colon cancer, a study on page 16 showed INPP4B may be involved in the formation of Microsatellite instability (MSI) status in colorectal cancer which suggested that there might be other mechanisms for the carcinogenic effects of INBB4P. Furthermore, INPP4B might play a dual role in gallbladder cancer, which is the latest to be discovered. We have added these new studies on page 21 and in Table 1.

Eventually, we provided decomposable Figures, and organized them into a single PowerPoint file. We confirm the figures are original, and we added the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©Han L et al. 2023.

We would love to thank you for allowing us to resubmit a revised copy of the manuscript and we highly appreciate your time and consideration.

Have a nice day and look forward to your reply soon.

Best regard.

Le Han, Shi-Yu Du, Shuo Chen

China-Japan Friendship Hospital

August 17, 2023