Dear editors,

Thank you for your reply and for the reviewers' comments concerning our manuscript entitled "Integrative analysis of the inverse expression patterns in pancreas development and cancer progression" that we submitted to *World Journal of Gastroenterology*. Those comments on our study are insightful and we feel they have led to significant improvement of our paper.

We have revised our manuscript according to the reviewers' suggestions. The following is a point-by-point response to the reviewers' comments and questions.

Reviewers' comments:

Reviewer #1 (Remarks to the Author):

Critique -This paper represents a basic study regarding the inverse gene expression patterns in pancreas development and pancreatic cancer progression. The authors studied 6 pancreatic cancer datasets collected form TCGA database to establish differentially expressed genes related to pancreas development and pancreatic cancer. Further, gene clusters with highly similar interpretation patterns between pancreas development and pancreatic cancer progression were established by SOM-SVD. The matrices with 1,257 genes, which obtained from this analysis, were clustered into four gene clusters. The cluster 2 and cluster 4 were highly expressed at the early stage, while they were identified as the continuously up-regulated expression patterns. In contrast, low gene interpretation was observed in cluster 1 and cluster 3 at the early stage and increased with time. So, they were identified as continuously down-regulated expression patterns. The whole idea seems very smart and indeed it is reasonable that during the pancreatic cancer developmental process, the same groups of genes which control the embryonic development of normal pancreas, probably interact, in a mutated status, and generate the abnormal proliferation of malignant cells. However, there are several recent papers referring to pancreatic cancer genetics, such as: Cicenas J, et al. Cancers 2017, 9, 42; doi:10.3390/cancers9050042, Knudsen ES, et al. Gut 2018;67:508–520, The Cancer Genome Atlas Research Network Cancer Cell 32, 185–203, August 14, 2017, and several other important papers in that topic, analyzing the various genomic characteristics of pancreatic cancer. The authors should refer to these recent papers in their Discussion and try to find relations with them. -The authors state that glycerophospholipid metabolism pathway plays an important role in pancreatic cancer tumorigenesis. The authors should add a comment analyzing the importance of this pathway, and probably the relative importance of the 3 or 4 most important pathways presented in Table 2. -The Core Tip of the paper should be minimized, whereas the Discussion should be enriched. -The whole paper should be seen and corrected. by an expert in English language and terminology.

[Response] We are grateful for reviewer's suggestions and we have compared our data with other works related with pancreatic cancer in the discussion section. We also discussed the relationship of steroid hormone biosynthesis with immunosuppressive tumor microenvironment and the role of citrate cycle in modulation of cancer cell proliferation. Additionally, we have revised our manuscript and corrected grammar errors.

Reviewer #2 (Remarks to the Author):

There are not specific comments to the authors as this is an investigated study based on the analysis of genes which are involved in the metabolic pathway of pancreas. Perhaps on limitation is related to the small number of pancreatic samples

[Response] We are grateful for reviewer's comments and we will add greater number of clinical samples in our future works.

Reviewer #3 (Remarks to the Author):

This paper discusses molecular interpretation patterns of pancreas development and cancer progression. The title is in accordance with the main subject/hypothesis of the manuscript, and the abstract and the key words reflect the main results of the article. The manuscript clearly explains methods in adequate detail. The statistical analysis in this paper is suitable for the goals of this study. The results show continuously dysregulated interpretation patterns in pancreas development and pancreatic cancer. The data obtained is discussed well, recent papers in this field are cited. The results obtained will be useful in the larger-scale development and integrative cancer analysis. The figures are appropriately illustrative of the paper contents, but the legends do not explain drawings in sufficient detail The manuscript is well written but needs minor language polishing. I suggest to accept the manuscript with minor revisions.

[Response] We are grateful for reviewer's suggestions and we have revised our manuscript and corrected grammar errors.

Reviewer #4 (Remarks to the Author):

This is an important paper tackling important issues in the future prognosis and treatment of pancreatic cancer. Rigorous statistical methods have been applied. It should be published. However, there are marked English grammar mistakes and the whole manuscript needs to be re-written by someone with excellent proficiency in English.

[Response] We are grateful for reviewer's suggestions and we have revised our manuscript and corrected grammar errors.

Reviewer #5 (Remarks to the Author):

The manuscript by Tian and others represents a potentially valuable contribution to the interesting question referring to the connection between (normal) pancreatic development and pancreatic cancer development. Besides the idea that is excellent and intelligent, the work falls way behind the potential residing in the data. For once, one would like to know about the expression pattern of the target pathway in the pancreas - normal and diseased - beast done by obtaining the also publicly available data in the Human Protein Atlas. Upon superficial check I did, these molecules are expressed in the exocrine pancreas, yes, but in the acing compartment. This needs to be shown and discussed. Furthermore, there are some (admittedly few) data sets out there from PanIN and IPMN. To demonstrate and underscore the genetic evolution towards cancer, the paper would make a much better impact. If decided against it, it needs to be discussed. Minor issues: 1) reference missing last lane on p. 7 (page numbers are also missing!!) when referring to the SOM-SVD. 2) In several figures referring to red-blue colour coding is in a way misleading as part of the figure is a heat map which is red-green (as it is correctly depicted). The blue of course refers to the RIGHT part of the picture(s).

[Response] We are grateful for reviewer's suggestions and we have revised our manuscript and corrected errors in figure legends.