Reviewer #1:

We would like to thank the reviewer #1 for his/her valuable comments on the manuscript. To address the concerns raised, a new Figure has been added. Changes to the text are underlined and highlighted in red.

The manuscript submitted by Seimiya et al is a review about inflammation and differentiation in pancreatic cancer. This review is interesting and well written. I have few comments:

1. The authors discuss in the perspective section that Kras mutation and epigenetic regulation play important roles in pancreatic carcinogenesis. However, all references regarding reprogramming via gene regulation are related to autonomous or non-autonomous cell signaling. The authors should develop the epigenetic topic. When the authors described the crucial role of epigenetic, the reference is about ectopic expression of ptf1 and mst1.

Response: *We thank the reviewer for raising this critical issue. To respond to the reviewer's concern, we have added a new paragraph regarding the epigenetic topic in the revised manuscript, in addition to ectopic expression of ptf1 and mst1.*

2. Few important references should be added: - Raimondi S, et al., Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol. 2010 Jun;24(3):349-58. doi: 10.1016/j.bpg.2010.02.007. Review. This manuscript is a meta-analysis about PC, pancreatitis and its etiology. - Cazacu et al., Pancreatitis-Associated Genes and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis. Pancreas. 2018 Oct;47(9):1078-1086. doi: 10.1097/MPA.0000000000001145. Another meta-analysis about genes associated with pancreatitis and PC. This could be included next to the PRSS1 paragraph.

Response: *We appreciate the reviewer's suggestion. We have added the references and referred to the relationship between PRSS1 (SPINK1) gene mutation in hereditary pancreatitis patients and the risk of pancreatic cancer, in the revised manuscript, according to the reviewer's comments.*

3. Wnt and Hippo pathways should also be included in the figure 1. The pancreatic differentiation is a little bit over-simplified. The authors should cite the excellent review of Shih et al., Pancreas organogenesis: from lineage determination to morphogenesis. Annu Rev Cell Dev Biol. 2013;29:81-105. doi:

10.1146/annurev-cellbio-101512-122405. Notably, see the figure 3 that remind the figure 1 of the present manuscript.

Response: *We appreciate the reviewer's suggestion. We have included the Wnt and Hippo pathways in the figure 1 and added the review by Shih et al. in the revised manuscript.*

4. I suggest adding a figure about autonomous and non-cell autonomous intracellular signals involved in inflammation that are described in the manuscript. This would be helpful and give an overview of this topic.

Response: *We appreciate the reviewer's suggestion. We have added a new figure about autonomous and non-cell autonomous intracellular signals involved in the inflammation that are described in the manuscript, according to the reviewer's suggestion.*

5. Bailey et al (Nature 2016) described a subtype of PDAC that are immunogenic tumours containing upregulated immune networks. This could be discussed in regards with inflammation and chronic pancreatitis.

Response: *We appreciate the reviewer's suggestion. We have added a paragraph about immunogenic subtype of pancreatic cancers, in the revised manuscript.*

Minor points: Page 11: "From these results, cell differentiation status at the embryonic stage or adult stage may control end organ carcinogenesis.", "end"? I guess the correct sentence is "May control organ carcinogenesis"

Response: *We apologize for our carelessness and thank the reviewer for pointing this out. We have corrected the sentences.*

We thank the reviewer #1 for the constructive and insightful comments, which have helped us to substantially improve our manuscript.

Reviewer #2:

We would like to thank the reviewer #2 for his/her valuable comments on the manuscript. To address the concerns raised, a new Figure has been added. Changes to the text are underlined and highlighted in red.

The authors of the review paper entitled "Inflammation and de-differentiation in pancreatic carcinogenesis" took up an interesting and difficult subject at the same time. However, already in the abstract of their manuscript, they indicate the potential contribution of the process of de-differentiation in cancer development. Despite some information about the process of de-differentiation, at the moment, the potential impact of stem cell damage as a factor responsible for the process of carcinogenesis is being considered. Many of the mechanisms proposed by the authors as a responsible for pancreatic cacner development are well-known and described in the literature as a general mechanisms of carcinogenesis e.g. K-ras mutation and colon cancer. Moreover, I would like to point out that impaired differentiation is not the same as de-differentiation.

Response: *We thank the reviewer for raising this critical issue. According to the reviewer's suggestion, we have mentioned the potential involvement of stem cell damage as a factor for pancreatic carcinogenesis. Also, we carefully used the terms "impaired differentiation" and "de-differentiation" in the revised manuscript, as the reviewer suggested.*

There are some inaccuracies in the text. The background in case of HPV induced cervical cancer is not inflammation related but rather genetic. The cancerogenesis depends on the loss of esxpression of E2 viral gene when incorporated to the eucariotic genome of infected cells. E2 plays a role of E5 gene repressor, which is a growth regulator.

Response: *We apologize for our inaccuracies about HPV-induced cervical cancer and thank the reviewer for pointing this out. We have corrected the sentences in the revised manuscript.*

Described mutation in PRSS1 gene, especially 356 G>A incerase autocatalitical property of trypsinogen and therefore accelerate convertion to trypsin and intrapancreatic action. So there is no connection with regulation of the cell cycle.

Response: *We agree with the reviewer's opinion. In our revised manuscript, we did not describe the connection between PRSS1 gene and the regulators of the cell cycle.*

In some cases authors draw conclusions with poor literature support. The statement that "These results suggest that the carcinogenic potential through genetic mutation

differs between the embryonic and adult stages in mice″ might also sugest and support the thesis that only stem cells and their disfunctions are responsible for carcinogenesis.

Response: *We thank the reviewer for raising this critical issue. We have added the description about the potential involvement of "stem cell damage and impaired differentiation", in addition to the "de-differentiation" during the carcinogenesis steps, in our revised manuscript.*

TH17 lymphocytes are widely known and associated with many inflammatory conditions, not only pancreas but, above all, colon.

Response: *We thank the reviewer for pointing this out. We mentioned the involvement of Th17 in inflammatory conditions in other tissues as well as in pancreas, in the revised manuscript.*

In my opinion the entire chapter on pancreatic organogenesis is unnecessary, and the WNT and Hippo pathways described in it are widely known as involved in the differentiation of all organs.

Response: *We thank the reviewer for this suggestion. However, because we believe that the chapter on pancreatic organogenesis, especially hierarchical differentiation processes, would help readers to understand the transcriptional changes during de-differentiation (and carcinogenesis), we intentionally remained the chapter as it was. Also, we have included Wnt and Hippo pathways in the figure 1 according to the reviewer #1's comments, which, we hope, would help the readers to understand the entire chapter.*

In addition, the authors have very superficially included the contribution of epigenetic factors in the process of neoplasm pancreatic carcinogenesis.

Response: *We thank the reviewer for raising this important topic. To respond to the reviewer's concern, we have added the explanation about the roles of chromatin remodeling factors as a new paragraph, in the revised manuscript.*

We thank Reviewer #2 for the constructive and insightful comments, which have helped us to substantially improve our manuscript.