

Dear Editor,

We are pleased that You offered us an invitation to revise our work. We hope that our revision, based on the input of the reviewer and Science Editor is satisfying.

Best regards,  
the Authors.

---

Reviewer #1

**Reviewer:** Manuscript 63332 by Cacati et al. and entitled “Effects of CXCL12 isoforms in a pancreatic pre-tumour cellular model: microarray analysis” concerns a microarray analysis of the response of a model cell line for very early, pre-tumor pancreas, the hTERT-HPNE E6/E7/KRasG12D cell line which mimics PanIN-3 phase of pre-maglinant progression. Stromal cancer associated fibroblast (CAFS) are well known to secrete extracellular matrix components and thus contribute to the well known dense stromal compartment (desmoplastic reaction) in pancreatic adenocarcinoma (PDAC). These cells also secrete cytokines that can modify the behavior not only of the cancer cells but also drive the pre-cancer cells to progress. One group of these cytokines are the CXCL12 family members. The authors performed these experiments to determine the role of a series of CXCL12 family members ( $\alpha$ ,  $\beta$ , and  $\gamma$ ) in modifying the cells gene expression and motility to drive the early steps of progression. They found differences in expression of cell cycle genes by the  $\beta$  isoform while all there isoforms affected genes for the cytoskeleton, adhesion and migration. Interestingly, the  $\gamma$  isoform showed a higher induction of migration in a wound healing assay than did the other two isoforms. The manuscript is very well organized and the data well presented and clearly discussed.

**Authors:** Thank you very much. We are grateful for Your time and effort in reading our paper.

**Reviewer:** As this paper will be read by those not so familiar with the details of PDAC and pancreatic intraepithelial neoplasia progression, I feel that a more complete description of the hTERT-HPNE E6/E7/KRasG12D cell line be presented both in the M&M and especially in the Discussion in-order to have a better idea of this cell line. We need to know at least some details of how the KRasG12D expression/transformation is considered to modify the original cell line.

**Authors:** We agree with the referee, thus we have modified Material and Methods and Discussion sections in order to better describe this cell line and the role of KRAS in PanIN and PDAC.

**Reviewer:** Also, there are some small problems with English throughout the manuscript that needs to be corrected; just a few examples: Abstract: “highlighted that only the expression of few genes was affected.” should be “the expression of only a few genes...” “At functional level,  $\beta$  isoforms altered the expression of genes mainly involved in cell cycle regulation.” Please remove “At functional level” since this not functional Introduction: “An earliest genetic event” should be either ‘An early’ or ‘The earliest’ Conclusions: “different CXCL12 isoforms prompt cell migration at different extents” should be: “to different extents”. These may seem to be small errors but together with other examples, this makes the reading difficult and is a shame in such a good manuscript.

**Authors:** We are sorry. Now, the problems that You pointed out have been fixed. We also fixed other issues and long sentences.

---

Science Editor:

**Science Editor:** (1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

**Authors:** We are sorry. Now, we have uploaded also this document.

**Science Editor:** (2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

**Authors:** Now, we have uploaded also this file in .ppt format.

**Science Editor:** (3) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text; and

**Authors:** We are sorry. Now, we have written also this section.

**Science Editor:** (4) Authors should always cite references that are relevant to their study. Please check and remove any references that not relevant to this study.

**Authors:** We checked: all references are relevant.