Reviewer's report

Title: Angiotensin II type 2 receptor signaling significantly attenuates growth of murine pancreatic carcinoma grafts in syngeneic mice

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Reviewer: Martin Fernandez-Zapico

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The study by Doi et al evaluates the role angiotensin II type 2 receptor (AT2R) signaling on the growth of pancreatic tumors in a murine AT2R knockout (AT2R KO) syngeneic model. The authors found an increase growth rate in pancreatic tumor containing fibroblast from AT2R KO as compared to the wild type ones. The proliferation index was higher in the AT2RKO tumors and apoptosis levels were reduced in this group. Similarly, co-culture experiments using AT2R KO fibroblast show increased pancreatic cancer cell growth as compared to the groups cultured with wild type fibroblast. Together, these results led the authors to conclude that AT2R plays a role in pancreatic carcinogenesis by regulating the stromal compartment and it is a potentially important target for chemotherapy for this tumor.

This is a very interesting and novel study testing the role AT2R in pancreatic cancer stromal compartment. However, there are few small aspects of the manuscript that are still premature for publication. I would like the authors to address the comments posted below before considering the manuscript for publication. Previous reports have shown increase VEGF production by the ATR2 signaling activation and suggested an oncogenic function for this pathway. The authors should determine the vessel density by immunohistochemical methods and expression VEGF in the different experimental groups. A paper by Anandanadesan R et al suggested the activation of MAPK pathway by ATR2 in pancreatic cancer. Comments about these findings as well as the potential role as tumor suppressor or oncogene in these tumors should be added to the discussion. Finally, the effect of AT2R deficiency on the fibroblast function should be further characterized. For instance, what is the effect on fibroblasts proliferation? The H/E staining showed increased fibrosis. The authors should determine the fibrotic index by immunohistochemistry and discuss potential implications for pancreatic tumorigenesis.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests