

Reviewer #1: The manuscript is exceptionally well-written by talented scientists. It's rare to meet so informative material of excellent quality with good language at the same time. I highly recommend everyone to get acquainted with the contents of the manuscript and, of course, it definitely deserves to be published.

**Respond:** Thanks for your review!

Reviewer #2: Hereby I would like to comment on the article entitled: "Multiple Roles for Cholinergic Signaling in Pancreatic Diseases" by the authors Junmin Yang et al et al. The authors present a review of the literature on the role of cholinergic signalling in pancreatic disease. This is a well-written manuscript with an important topic. I have some comments: The authors divide pancreatic disease in acute and chronic pancreatitis and PDAC. The part on PDAC seems not integrated in the rest of the manuscript. The authors could choose to address the interaction of cholinergic signalling on inflammation and cancer more specifically. As a reader it may also help to have a figure showing the different effects. Some of the text is divided between acute and chronic pancreatitis, for example the part on alcohol consumption. I would integrate these parts and describe the effects on acute and chronic pancreatitis in the same paragraph.

**Respond:** Thank you for your suggestion. We have added the relationship between acute pancreatitis and chronic pancreatitis and discussed the role of alcohol in the chapter on chronic pancreatitis. In the chapter on pancreatic cancer, we have added a discussion of the potential mechanisms of cholinergic nerves in the transformation of chronic pancreatitis to pancreatic cancer. Finally, we've added a table for better understanding.

Reviewer #3: Dear Authors, Thank you for sharing your experiences on pancreatic diseases and your article entitled "Multiple Roles for Cholinergic Signaling in Pancreatic Diseases" The article is written in good quality and

scientific manner. The topic is important and should be heard by other scientist and doctors. I recommend in publishing article. Sincerely.

Respond: Thanks for your review!

Reviewer #4: This review describes on the progression and role of cholinergic signaling in pancreatic diseases. Please show the cited literature to the reader in an easy-to-understand manner using figures and tables.

Respond: Thank you! We have added a new table at the end of the manuscript showing the different mechanisms of action of cholinergic signaling in pancreatic diseases, combined with figure to facilitate the reader's understanding.

Reviewer #5: This article is a review of the involvement of signals from cholinergic nerves in the development of acute pancreatitis, chronic pancreatitis, and pancreatic cancer, based on the activity of cholinergic nerves and their receptor distribution. It is well summarized, describing what is known to date about the association of each disease with cholinergic innervation. Patients with chronic pancreatitis are several times more at risk for pancreatic cancer than healthy individuals. Chronic pancreatitis is not mentioned as a risk for pancreatic cancer in this report, and it would be better if the relationship between chronic pancreatitis, cholinergic nerves, and pancreatic cancer is described. Also, the magnification of the pathology photos in FIGURE should be stated. It would be easier to see if the photos were posted in a larger size.

Respond: Thank you! We have incorporated the relationship and impact of chronic pancreatitis to pancreatic cancer in the chapter on pancreatic cancer, adding a new discussion of the mechanisms underlying the transformation of chronic pancreatitis to pancreatic cancer through cholinergic signaling. We have made appropriate changes to the figure, thank you for your suggestion!