Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "TBL1XR1 induces cells proliferation and inhibit cells apoptosis by PI3K/AKT pathway in pancreatic carcinoma" (ID: 54532). We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The responds to the reviewer's comments are as flowing:

Responds to the reviewer's commentsG:

Reviewer #1:

1, Please impact clinical relevance in this study. How were the effects of TBL1XR1 inhibitors for the patients with pancreatic carcinoma?

Respond: We thank the reviewer for the nice comment. We discussed the clinical significance of TBL1XR1 which marked in red in the discussion part.

2, Please summarize figures.

Respond: We thank the reviewer for the nice comment. We have adjusted it in our paper.

Reviewer #2:

1.This manuscript, 4532, reports the results of studies on the expression of TBL1XR1 and its function and the mechanism of action in pancreatic carcinoma (PCa) development. Based on the obtained the conclusion is that the patients with TBL1XR1-positive tumors has much worse overall survival rate than those with TBL1XR1-negative tumors. Moreover, it is shown that TBL1XR1 promotes PCa tumor cell growth through PI3K/AKT signaling pathway. While the presented results certainly support the reached conclusion, it should be noted that the role of AKT in cNOS activation through phosphorylation was not explored at all. This is a serious omission, since cNOS activation through Akt induced phosphorylation plays very important role in cell apoptosis as well as in the cellular signaling (see Inflammopharmacology, 18 (2010)233 – 240 and ISRN Gastroenterology 2011, doi.org/10.5402/2011/308727). Certainly, these papers should be incorporated into the revised paper. In addition,, the paper requires some language and grammar corrections (see Discussion "PI3K/AKT signalig pathway is participated in TBL1XR1-increase.."), instead participates…

Responds: We thank the reviewer for the nice and professional comment. We corrected our language and grammar mistakes which marked in red. We are grateful for the suggestion of illustrate the role of AKT in cNOS activation through phosphorylation. We red the two papers" Role of constitutive nitric oxide synthase S-nitrosylation in Helicobacter pylori-induced gastric mucosal cell apoptosis: effect of ghrelin" and "Helicobacter pylori Induces Disturbances in Gastric Mucosal Akt Activation through Inducible Nitric Oxide Synthase-Dependent S-Nitrosylation: Effect of Ghrelin", we have learned a lot from it. In our study, we used AKT inhibitor LY294002 to investigate AKT function, which could also get the similar results. At meantime, we discussed and cited these two lieratures in our paper.

Reviewer #3:

Comments 1. The types of pancreatic carcinoma should be clearly addressed according to the WHO.

Respond: We appreciate the reviewer for the nice comment. We have modified it according to your opinion.

2. TABLES 1 through 3: The headline 'Histopathological subtypes' is not correct. The authors give not the entities, but the grading and it comes not clear the grading of which type of pancreatic carcinoma.

Respond: We appreciate the reviewer for the nice comment. We have modified it according to your opinion.

3. A two-based category for grading should be used: low and high grade.

Respond: We appreciate the reviewer for the nice comment. We have modified it according to your opinion.

4. Figure 1 B: the TBL1XR1 expression is shown in lymphocytes and not in tumor cells. This point is of high importance. The source of TBL1XR1 should be identified in the tissues and better correlated to the findings in cell culture. How does the authors verify that cancer cell but not lymphocytes are under investigation?

Respond: We appreciate the reviewer for the nice and professional comment. We ask the pathologist to help us identify it as pancreatic cancer by HE staining. And we rearranged the Fig 1B.

Reviewer #4:

1.The authors investigated TBL1XR1 in pancreatic cancer with clinic-pathological data, and cell experiments. The results were rationale, but construction of the manuscript was immature. The logical flow to TBL1XR1 was not fully clear. How did the authors focus TBL1XR1 remained unclear. How was informed consent was obtained?

Respond: We red literature research and found that TBL1XR1 plays an important part in cell growth, anti-apoptosis, inflammation and transcriptional activation. And currently, researchers focus on the effect of TBL1XR1 in carcinogenesis and tumor progression, including nasopharyngeal carcinoma, colon cancer, gastric cancer, prostate cancer, breast cancer, and hepatocellular carcinoma. So we speculated that TBL1XR1 might function in pancreatic cancer, and luckily, we found TBL1XR1 induces cells proliferation and inhibit cells apoptosis by PI3K/AKT pathway in pancreatic cancer by in vivo and in vitro experiments. We get patients' approval of their pathological tissue for scientific research before surgery.

2.Materials and Methods was immature. This part should be revised so that the other researchers could repeat.

Respond: We appreciate the reviewer for the nice comment. We adjusted this part according to reviewer's opinion.

3.Methods of immunostaining was absent. How was the primary antibody obtained? Did "1640 medium" mean "RPMI1640"? Cell transfection. The amount of nucleic acid was not clear. Lentivirus-mediated RNA interference. Did the authors construct lentivirus vector for RNAi? If so, the transduction methods should be written. Was lipofectamine necessary for lentivirus transduction? What was CCK-8? Was it commercially available? Company names and locations of antibodies were absent. Table 1. TNM staging correlated with positivity of TBL1XR1. But tumor sized did not. Were there any speculations to this discrepancy? Figure 1B. Both adjacent and PCa tissues look accumulation of lymphocytes. Were there any other photos? For example, adjacent tissues include acinus, islets, and pancreatic duct. Pancreatic cancer tissues include cancer cells.

Respond: We appreciate the reviewer for the nice comment. We supplemented the methods of immunostaing, cell transfection and antibody information in the article. "1640 medium" means "RPMI1640", and we have adjusted it. The lentivirus vector was constructed by

Shanghai Genechem company and we rewritten the method in the artical.CCK-8 is widely used in the rapid and highly sensitive detection of cell proliferation and cytotoxicity based on wst-8, and we bought it from Shanghai Beyotime company. TBL1XR1 did not correlated with tumor size but with TNM staging, we thought it might due to the effect of lymphatic and distant metastasis. We rearranged the Fig 1B.

Reviewer #5: Good work. Congratulations. The authors have evaluated the role of TBL1XR1 in pancreatic cancers. By tissue assay and in vivo tests, they found that the receptor is associated with tumour progression as well as worse prognosis in pancreatic cancers.
Responds: Thanks for the reviewer's recognition of our work