Dear Dr. Ma,

First of all, thank you very much for your letter and advice. We have revised the manuscript, and would like to re-submit it for your consideration. We have addressed the comments raised by the reviewers, and the amendments are highlighted in red in the revised manuscript. Point by point responses to the reviewers' comments are listed below this letter.

We hope that the revised version of the manuscript is now acceptable for publication in your journal.

I am looking forward to hearing from you soon.

With best wishes,

Yours sincerely,

Ying-Ying Qiao

We would like to express our sincere thanks to the anonymous reviewers for their constructive and precious comments.

Replies to Reviewer 1

Comment 1: As the authors state, there have been reports implicating IL-22 in acute pancreatitis – although in different models. This restricts somewhat the novelty of their findings.

Answer: Reviewer 1 thinks that some researchers have investigated the effect of IL-22 on acute pancreatitis which would reduce the innovation of our findings. IL-22 has generated considerable interest in recent years, making it one of the best-studied members of the IL-10 family of cytokines. At present, most studies support a protective role for IL-22 in the prevention of pancreatic damage. However, no reports have described the effects of IL-22 on SAP-induced MODS. In our previously submitted manuscript, we showed that recombinant IL-22 protected mice against L-arginine-induced SAP-associated lung injury by enhancing the expression of anti-apoptosis

genes through the STAT3 signaling pathway. We are also exploring the potential protective effect of exogenous recombinant IL-22 on SAP-associated renal injury and SAP-associated liver injury with the similar method. We hope our work can provide a new vision for further research on the problem of complications of acute pancreatitis.

Comment 2: Only one model of AP was utilized, restricting generalizability of their findings.

Answer: Reviewer 1 requires that we should use different models of SAP in our study to increase the generalizability of our findings. The reviewer's suggestion is very constructive. In our previously submitted manuscript, we only use a mouse model of SAP induced by L-arginine to explore the role of IL-22 and its possible signaling pathway which reduces the universality of our research. There are several other SAP models we can choose to determine our findings. A mouse model of SAP induced by cerulein (Cn) and lipopolysaccharide (LPS) has been well-established. Another SAP model was induced in mice by the retrograde injection of 5% sodium taurocholate into the pancreatic duct. We should use these different models in our experiment to increase the scientificity of our results. However，due to limited laboratory conditions and fund support，We can't supplement this part of the experiment for the time being. We will complement the experiments in this respect once we received the funding.

Comment 3: To clearly delineate the effects of IL-22 in SAP, GEMMs should be utilized with IL-22 knockout or IL-22 receptor knockout (with the corresponding experiments).

Answer: Reviewer 1 requires that we should use transgenic mouse models of IL-22 knockout or IL-22 receptor knockout to determine the effects of IL-22 in

SAP-associated lung injury. In our previously submitted manuscript, we only use a mouse model of SAP induced by L-arginine to explore the role of IL-22 and its possible signaling pathway which reduces the universality and precision of our research. The transgenic mouse models provide a powerful tool for studying the molecular mechanism of human diseases. We can use transgenic mouse models of IL-22 knockout or IL-22 receptor knockout to further explore the role of IL-22 and this, without doubt, will increase the accuracy of our conclusions. However, these transgenic mouse models are very expensive, and we are short of fund support now. We will complement the experiments in this respect once we received the funding.

Comment 4: IL-22 is injected before SAP onset, limiting the clinical applicability of their findings. The authors should at least include some experiments with therapeutic IL-22 application.

Answer: Reviewer 1 requires that we should explore the therapeutical effect of IL-22 by giving rIL-22 after the model was established so as to increase the clinical applicability of their findings. In our previously submitted manuscript, we investigate the potential protective effect of rIL-22 on SAP-associated lung injury in mice by injecting IL-22 subcutaneously before SAP onset which limits the clinical applicability of our findings. In our experiment, IL-22 was demonstrated to alleviate acute severe pancreatitis associated acute lung injury in mice by enhancing the expression of anti-apoptosis genes such as Bcl-2 and Bcl-xL, through the STAT3 signaling pathway. This is a preliminary exploration of the functions of IL-22. Next, on this basis, we will carry out further research to determine the therapeutical effect of IL-22 by giving rIL-22 after the model was established. But now， due to limited laboratory conditions and fund support，We can't supplement this part of the experiment. We will complement the experiments in this respect once we received the funding.

Comment 5: The authors speculate about apoptosis. This could have been easily tested on tissue sections and would have further supported the authors' conclusions.

Answer: Reviewer 1 requires that we should test epithelial/endothelial cell apoptosis on the lung tissue sections in order to further support our results. In our previously submitted manuscript, we found that mice with SAP associated lung injury were responsive to rIL-22 administration by enhancing the expression of anti-apoptosis genes such as Bcl-2 and Bcl-xL through the STAT3 signaling pathway. Apoptosis is a key mechanism causing cell death and organ diseases, and failure of apoptosis is contribute to the recovery of tissue damage. TdT- mediated dUTP nick end labeling (TUNEL) is a method of choice for rapid identification and quantification of the apoptotic cell fraction in the tissue sections. We should use this method in our study to increase the accuracy of our results. However，due to limited laboratory conditions and fund support，We can't supplement this part of the experiment for the time being. We will complement the experiments in this respect once we received the funding.

Comment 6: Figure 2: why not all time points for the rIL-22 group? Same for figures 3 and 4. These data should be included. Figure 5: it is again not clear, why not all time points were analyzed in 5D.

Answer: Reviewer 1 requires that the data at 24 h, 48 h, and 72 h after the administration of L-arginine in rIL-22 group should also be analyzed. In our previously submitted manuscript, rIL-22 (200 ng/per, 5 times) was administered subcutaneously to mice at indicated times in the rIL-22 group (Figure 1). In the course of the whole experiment, each mouse received 1ug rIL-22 treatment. At 24 h and 48 h after the injection of L-arginine, the mice in rIL-22 group hadn't received complete treatment. For this reason, we only

analyzed the data at 72 h after the administration of L-arginine. By compared the results in SAP group at different time points, we found that the severity of pancreatic and lung injuries became maximal at 72 h after injection of L-arginine and this is another reason for us to analyze data at this point in different groups.