We had revised the manuscript according to the editor's opinion.

1. Peer 1- # 00646291

"The experiments assessing the role of GR in the regulation of the miR-22 expression should be performed in the presence and absence of dexamethasone."

The AR42J cells, which originally have exocrine properties, secrete a large amount of amylase. The use of dexamethasone can change the secretory properties of AR42J cells. Our further research is to explore the treatment measures of AP by using another drugs targeting GR in vitro cell model and in vivo AP model.

Peer 2 - #03459514

1. "Pancreatic AR42J cells are an amphycrine type of cell. Prior to performing exocrine studies the cells must be differentiated by incubation in the presence of dexamethasone. It is not mentioned in the manuscript whether the authors carried out this procedure prior to the stimulations."

   The AR42J cells, which originally have exocrine properties, secrete a large amount of amylase, which can be characterized by double secretion after glucocorticoid treatment. So we did need to incubate in the presence of dexamethasone.

2. "miR-22 primer sequence is missing. This information must be given in the manuscript. "

   The miR-22 primer was designed and synthesized by RiboBio, which has the patent of miRNA primers.

3. “It is not clear to the reader why determination of amylase release is carried out. It is not clear which relationship, if any, exists between the increase in amylase release and the pro-apoptotic effects of caerulein.”

   In this article, elevated amylase in the medium supernatant confirmed the property of AR42J cells and reflected the stimulation of AR42J cells by exogenous caerulein.

4. “Results section: The paragraph “AR42J cells were transfected with the miR-22 mimic as described. The expression of miR-22 was significantly elevated in the cells transfected with the mimic compared with the miRNA NC cells (Figure 2A). As shown in Figure 2B and 2C, the mRNA and protein expression levels of ErbB3, the target gene of miR-22, were significantly lower in cells overexpressing miR-22 than in the control cells” is complicated to understand. mRNA and protein expression levels of ErbB3, the target gene of miR-22, were significantly lower in cells overexpressing miR-22: is this right? The information given seems controversial in the way the information is written. One would expect an increase in the mRNA and protein expression levels of ErbB3 with upregulation of miR22.”

   Our previous study showed that ErbB3 was a target gene of miR-22. Up-regulation the expression of miR-22 could repress ErbB3 expression. We confirmed this point in this article.

5. “Separately miR22 and Cae induce apoptosis. And the same is observed with their combination. It is not clear why the authors use the combination of both to study cell death and the relevance of these observations to get a conclusion. A comparison between the effects of miR22 alone and that of miR22 plus Cae should be carried out in order to see if the effect is additive.”

We add the miR-22 mimic group protein level in the result.

6. "It would give important information to study the effect of Cae on Nr3c1 expression, bearing in mind the action of Nr3c1 on miR22 expression. Moreover, the relationship between miR22 and Cae needs to be better explained. Specially, because the authors state that the upregulation of miR-22 promoted Cae-induced apoptosis of AR42J cells."

   In further study, we will illuminate the relationship between Cae and Nr3c1.

7. "In the results section the authors mention that the transcription factor Nr3c1 regulates the expression of miR-22. However, later on it is stated that ErbB3 is the target gene of miR-22, and that it is repressed. This information leads the reader to misunderstanding and needs clarification."

   Our result showed that miR-22 might promote Cae-induced apoptosis of AR42J via down-regulating the expression of its target gene, ErbB3, and PI3k/Akt signaling pathway. Glucocorticoid receptor transcriptionally repressed the expression of miR-22 by binding to the miR-22 promoter transcription start site. The upregulation of miR-22 expression resulting from silencing Nr3c1 contributed to the apoptosis of AR42J cells.

Peer 3 - # 03257477

1. "Analysis of phosphorylated proteins by W-blot, specifically PI3K and Akt, requires the normalization of densitometry with total proteins besides a constitutive protein."

   We add total PI3K and Akt protein levels in the result.

2. “Discuss deeply how the fact of overexpressing the Nr3c1 gene in absence of the ligand is enough to diminish the transcriptional activity of miR-22. This glucocorticoid receptor has a cytoplasmic location and, upon ligand binding, is transported into the nucleus.”

   Our studies had demonstrated that GR transcriptional repressed the expression of miR-22. Further investigations need to be performed to study the underlying mechanism.

3. “Besides authors´ previous work, other studies have demonstrated the effect of miR-22 over apoptosis and its mechanistic effects (v.g. Pant (2017) Butyrate induces ROS-mediated apoptosis by modulating miR-22/SIRT-1 pathway in hepatic cancer cells. Redox Biology; Lv (2018) MiR-22-3p Regulates Cell Proliferation and Inhibits Cell Apoptosis through Targeting the eIF4EBP3 Gene in Human Cervical Squamous Carcinoma Cells. Int J Med Sci). These studies must be mentioned in the discussion and it would be desired to put in the recent literature context the novel results of the present work.”

   Some studies had demonstrated that miR-22 could inhibit the apoptosis of human cancer cells, which had little relationship with our study. So we did not discuss in our manuscript.

4. “The effects over PI3K, Akt and apoptosis markers with si-Nr3c1 without Cae are necessary to see the effect without inducing apoptosis with Cae.”

   Our results showed that the up-regulation of miR-22 could promote caerulin-induced apoptosis of AR42J cells, while the apoptosis of AR42J cells were not obvious without caerulin. So we did not set a group of si-

Nr3c1.

5. “The measurements of amylase are little discussed. For example, what is the power of these quantifications? How authors explain differences in amylase concentrations between treatment with Cae and missing of differences in the presence of si-Nr3c1 or miR-22 mimic.”

   In this article, elevated amylase in the medium supernatant confirmed the property of AR42J cells and reflected the stimulation of AR42J cells by exogenous caerulein.