Answering reviewers:

Reviewer #1 (00253974): The review "Acinar Cell Injury by Inadequate Unfolded Protein Response in Acute Pancreatitis" by Barrera et al. gives a summary about the current knowledge of an inadequate unfolded protein response (UPR) as the crucial inflammatory injury regulator in acute pancreatitis (AP) and thereby emphasizes the importance and need for further research and management of AP. In doing so, the authors give a good overview over the relevant literature in that field and were able to describe it in a well-written and understandable way. Furhtermore, they managed to stress out the clinical relevance beyond the complex molecular mechanistic background and provide approaches for research and clinical management of AP. Also the figures are well-designed and presented.

Response: We greatly appreciate Reviewer#1's comments.

Reviewer #2 (02441161): A very good review which could help facilitate the research and management of acute pancreatitis.

Response: We greatly appreciate Reviewer#2's comments.

Reviewer #3 (00052339): Acinar Cell Injury Induced by Inadequate Unfolded Protein Response in Acute Pancreatitis Kaylene Barrera et al Reviewer's comments: This manuscript described the molecular mechanisms of injury of acinar cells in acute pancreatitis. The author emphasized the role of the unfolded protein response (UPR) of ER and designated the activation of UPR in the intracellular signaling pathways. As some points are not clarified, the following points should be addressed: #1 We would like to know the essential differences between the adequate and inadequate (or dysregulated) UPR activation in Fig.2. In addition, The NFκB may be one of down stream target of UPR signaling. How does NFκB differentiate the survival or toxic signals in response to adequate or inadequate UPR signal? #2 In Fig.2 and 3, active and ineffective were shown as a solid and dotted line, respectively, however, there was word "ineffective" in the context sentences. In the section of PERK/eIF2α/ATF4, for example, there were only the terms of "Activated PERK", "over-activation of PERK/eIF2α/ATF4" and "Activation of PERK/eIF2α/ATF4".

Response: We greatly appreciate Reviewer#3's constructive suggestions, which helped us to make our manuscript better.

In order to address his/her #1 concern, we have made following modifications: **(1)** the original description of Fig2 in the context, "As shown in Figure 2, we propose that adequate UPR induce basal NFκB activity to enhance the survival of acinar cells, while in dysregulated UPR, highly active PERK, IRE1 and ATF6 significantly upregulate NFκB's activity to promote the inflammatory response in AP", has been changed to "As shown in Figure 2, we propose that adequate UPR induces basal NFκB activity to enhance the survival of acinar cells since except IRE1/IKK, neither PERK/eIF2α nor ATF6/AKT is effective in inducing the degradation of IκBα. In dysregulated UPR, however, all three pathways are activated to effectively promote IκBα degradation. This results in significantly upregulated NFκB's activity, which promotes the inflammatory response in AP", and **(2)** details of IκBα degradation and NFκB activation have been added in Fig2 to more accurately illustrate how NFκB's pro-inflammatory signaling is activated by inadequate UPR.

To address his/her #2 concern, we have added "effective" and "effectively" in the context sentences to make the description consistent in the context and in the figure legends. For example, in the description of Fig2, "neither PERK/eIF2α nor ATF6/AKT is **effective** in inducing the degradation of IκBα. In dysregulated UPR, however, all three pathways are activated to **effectively** promote IκBα degradation. This results in significantly upregulated NFκB's activity, which promotes the inflammatory response in AP", and in the description of Fig3, "while the protein degradation is attenuated because of the lack of enough XBP1 to **effectively** process cathepsins".

Reviewer #4 (03316963): The authors reviewed the relevant literatures and propose the mechanistic models in the hope of facilitating the research required for the development of effective AP treatment. The novelty is good, and the references were enough to reflect the advancement of the AP treatment.

Response: We greatly appreciate Reviewer#4's comments.