Dear editors and external reviewers:

First of all, thank you very much for your recognition, evaluation and guidance of the study, your very constructive and valuable comments not only prompted this paper to be more rigorous and improved, but also for us to engage in more rigorous academic research in the future and very much of guiding value. We sincerely thank you!

Our group found that Gasdermin D-mediated hepatocyte pyroptosis plays an important role in the pathogenesis of ALF,which was published in “World Journal of Gastrointerology”. Furthermore, we combined with ferroptosis to further explore the mechanism of acute liver failure and the potential therapeutic targets of acute liver failure. Based on the above further continuous research, we have revised it according to the reviewer's suggestions. In accordance with the opinions of the three experts, we have conducted a serious discussion, and this note.

Recommendations from Expert 1 (07540117):

For the first time, about studying the role of other pathways in ALF, this is the direction of our group's next research. Secondly, the issue of relatively small sample size and potential risk of drugs that you mentioned, teacher, is indeed one of the limitations of this paper. Thank you, for your report comments.

Recommendations from Expert 2 (06400386):

Firstly, male GSDMD-/- mice are systemic knockout. secondly, we can provide pictures of the liver samples in Figure 2. And thirdly, regarding how it is seen in the H&E staining that pifithrin-α or liproxstatin-1 is associated with structural damage in pre-treated GSDMD-/- mice, it is mentioned in the results section of the paper that compared to the model group, the results of pifithrin-α or liproxstatin-1 and GSDMD-/- mice had less structural damage to the hepatic cord and most of the hepatic lobules were structurally intact. Thirdly, Figure 2D is trying to illustrate a point that we found that increased or decreased expression of GPX4 did not affect p53 but it acted indirectly by regulating GSDMD, suggesting that GPX4 is a downstream regulator of p53. Nevertheless, enhancement of GPX4 reduced p53 transcription, which is inconsistent with the western blot results. We speculate that the difference between mRNA and protein levels suggests that post-transcriptional regulation, translational efficiency, and post-translational modifications alter protein levels. One possible explanation is that reduced translational efficiency may be compensated by increased transcriptional activity. Lastly, the knocked down or overexpression of one protein, the WB result see supplementary material, thanks.

Recommendations from Expert 3 (06373083):

Thank you very much for your valuable comments, our next step will be to explore other mechanisms of acute liver failure and address the translational gaps, and we hope to make more in-depth contributions at the level of the mechanisms of acute liver failure occurrence.

Again, we are so sorry to bring you so much trouble because of our carelessness. At last, thank you for your review and your comments again. We are looking forward to hearing from you.

Your sincerely,

On behalf of all co-authors.
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