Dear editors,

We are very grateful for your and reviewer's advice regarding our manuscript. According to these advices, we have amended the relevant parts of the manuscript as follows. The manuscript has been re-edited, checked and corrected the grammar and spelling errors carefully throughout the full manuscript by a native English speaker. We have highlighted the changed part with red color in the revised manuscript.

Reviewer's advice

Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors:

1. The discussion part of the manuscript needs to be further concluded on its scientific value and clinical significance should be analyzed in depth, based on the experimental results and references, rather than simply summarizing previous research and repeating the experimental results. And there is lots of Typo's error don't meet the standard of this journal, such as: the reference [3] in the first paragraph of page 4 repeated marks （Page 4, line 13, and Page 4, line 17）; Figure 4 Effect of SGs on G3BP1 and ERS related molecules in hepatocyte hypoxia model through ERS (Page 22, line 2) etc.

Response: Thanks for your valuable suggestion. We have re-checked common spelling and grammar mistakes in the articles. We have also re-written the discussion part, added the description of another SGs marker (TIA-1), mechanism of the modeling agent LPS combined with D-Gal and characteristics of ALF mice, limitations of this study. Moreover, the significance of the experiment based on the specific experimental results was also discussed. In the result part, the significance of the specific groups and the research significance of each section are also discussed in turn, so as to make the article more fluent, so that readers can better understand the experimental process.

2. The specific experimental groups were not introduced in detail, which was difficult to understand. For example, the experimental groups presented in the results were not specifically described in the method section. No hypoxia+anisodamine group presented in Figure 3.

Response: Thanks for your valuable suggestion. In the first part of the results, we discussed the central pathogenicity of hepatocellular hypoxia during acute liver failure, so we used a hepatocellular hypoxia model to simulate this process in vitro. In the second part of the results, the grouping basis of the cell experiment was discussed, especially why the Arsenite intervention group should be set separately. in the third part, "Effect of SGs on apoptosis in hypoxia model through ERS", ATF4 is a key regulatory molecule in the process of ERS. Knockdown of ATF4 and the SGs inhibitor anisomycin showed an antagonistic effect on cell protection. In this part, the grouping was set to show that SGs can affect hepatocyte injury through the ATF4-mediated ERS pathway. In addition, due to the fact that the anisodamine, an inhibitor of SGs, is a cell lesion and superimposed liver injury caused by hypoxia, a poor cell status was observed in the hypoxia+anisodamine group, which influenced a series of subsequent molecular biological experiments. The hypoxia+anisodamine group is therefore not set.

3. The color resolution of the histogram was not high enough to tell, such as Figure 1G and 1H, Figure 2G and 2H, Figure 4D and 4C, Figure 6E and 6F.

Response: Thanks for your valuable suggestion. In order to be more clearly identified, the color resolution of the histogram was redrawn by using the black, white and gray tricolors

4. The criteria to determine the successful establishment of ALF mouse model was no introduction in the manuscript. Acute liver failure has a high mortality rate, and a large number of hepatocytes died, which was unfortunately not mentioned the cumulative mortality of mice in the relevant experimental groups in the manuscript. Secondly, the pathological changes of liver tissues in the three groups shown in Figure 5A are little different, and no significant liver cell damage is found in the model group, which is inconsistent with the pathological changes of high level ALT, TBIL and TUNEL shown later.

Response: Thanks for your valuable suggestion. We have added the criteria to determine the successful establishment of ALF mouse. Since LPS combined with D-Gal is different from other modeling agents, we discussed the principle of ALF induced by LPS combined with D-Gal. Moreover, we have added the survival curve in Figure 5G, the related figure legends were also written. The liver tissue pictures of the typical lesions have been re-selected, particularly for the HE staining images of liver tissue in the model group.

5. This paper focuses on the role of stress granules in acute liver failure. Stress particles are composed of mRNA and ribosomal proteins. Typical stress particles include TIA-1, G3BP, HuR, TTP, poly(A)mRNA, 40S ribosome subunit, eIF4E, eIF4G, eIF4A, eIF4B, poly(A) binding protein (PABP), eIF3 and eIF2 (PMID:29129640, PMID:34670846). In the experiment, only immunofluorescence detection of G3BP1 was used to label the stress particles. It is recommended to use more than two detection methods to detect the level of stress particles, such as laser confocal, western blotting, etc., to reduce the deviation of experimental results and increase the persuasion. In addition, despite the use of Ars and anisomycin in the intervention of stress granules, there is still no direct evidence to prove the influence of SGs on hepatocyte apoptosis.

Response: Thanks for your valuable suggestion. We have used immunofluorescence in the results to verify the expression of another important molecule TIA-1 in each group of cells or animals. Due to the limitation of picture space, we did not include western blot to detect the expression levels of G3BP1 and TIA-1 in the text. We have also attached the results of western blot for G3BP1 and TIA-1. As you mentioned, despite the use of Ars and anisomycin in the intervention of SGs, there is still no direct evidence to prove the influence of SGs on hepatocyte apoptosis. In the next studies, we will use more appropriate methods to directly detect the influence of SGs on hepatocyte.

6. In this manuscript, SGs were used to reduce hypoxia induced liver injury, while arsenite (Ars), as the agonist of SGs, plays a protective role in liver injury. However, in other research reports, arsenite can damage liver cells (PMID: 35998476, 19733843）. How to explain the contradictory results of arsenite's influence on liver injury in your

research and others' researches?

Response: Thanks for your valuable suggestion. Large doses of arsenite are toxic to hepatocytes, but the small doses of Ars used in this study are not toxic and can induce the production of SGs. In this report (PMID:19733843), intervention doses of arsenite were 2.5 mg/kg/day, 5mg/kg/day and 10 mg/kg/day, and there was no effect on the expression of AQP9 in liver after 3 consecutive days of intervention. And only after 9 consecutive days of intervention, it can affect the expression of AQP9 and liver tissue injury. In this study (PMID:35998476), $NaAsO_2$ solution at concentrations of 25, 50, and 100 mg/L in drinking water ad libitum for 24 weeks. Meanwhile, the IC50 concentration of $NaAsO_2$ on L02 cells was 40 μM. In the cell experiment of this study, the survival rate of L02 cells reached more than 90% at the intervention concentration of 10μM(PMID:35998476). At the same time, the 1mg/kg intervention dose used in animal experiments was used continuously for 3 days before modeling. Therefore, both the modeling dose and the modeling time in this study were lower than those reported in the above literature, and the dosage was safe.

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision

Specific Comments to Authors: Brief summary: The paper entitled “Stress granules inhibit endoplasmic reticulum stress-mediated apoptosis during hypoxia-induced injury in acute liver failure” confirmed that SGs could protect hepatocytes from hypoxia-induced damage during ALF by reducing ERS mediated apoptosis. The research was done really well, however, there are still some problems in the manuscript. I think the manuscript will be given further consideration after revision. Comments:

1) There are some writing errors in the manuscript that need to be corrected. For example: in “Cell culture and treatment” section, “The Hypoxia + Ars group was first treated with Hypoxia for 12 h, followed by hypoxia treatment for 12 h”. And then, “min” and “minutes” should be unified. “in vivo” should be italicized.

Response: Thanks for your valuable suggestion. The manuscript has been re-edited. We have checked and corrected the grammar and spelling errors carefully throughout the full manuscript by a native English speaker.

2) The immunofluorescence results should be listed in the statistical chart, rather than just visual observation.

Response: Thanks for your valuable suggestion. We have added the histogram for the immunofluorescence results in Figure 1G, 2G, 4C, 6B.

3) In the text, Ars is described as a agonist for SGs, but in figure legends, Ars appears to have become an inhibitor.

Response: Thanks for your valuable suggestion. We are very sorry for making such a low-level mistake. We have corrected the mistake in figure legends in Figure 2, Figure 5, Figure 6 in the manuscript.

4) The color of some histograms is very similar, which is not conducive to readers' judgment.

Response: Thanks for your valuable suggestion. In order to be more clearly identified, the color resolution of the histogram was redrawn by using the black, white and gray tricolors

5) The immunofluorescence diagrams in figure 4 have no scale bar.

Response: Thanks for your valuable suggestion. We have added the scale bar in the immunofluorescence diagrams in Figure 4.

If you have any further requirement, please let us know. Thank you very much.

Sincerely yours

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