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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 88684

Title: SIRT1 ameliorates acute liver failure by reducing ferroptosis and pyroptosis via the p53/GPX4/GSDMD axis

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 07540117
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Iran

Author's Country/Territory: China

Manuscript submission date: 2023-10-05

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-11-02 06:31

Reviewer performed review: 2023-11-15 10:15

Review time: 13 Days and 3 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript has several strengths. Firstly, the authors used a comprehensive approach to investigate the involvement of ferroptosis and pyroptosis in ALF, using both C57BL/6 mice and GSDMD knockout mice. Secondly, they pre-treated the mice with various drugs and then injected them with LPS and D-GalN before recording the animal survival rate. Thirdly, they found that pre-treatment with ferroptosis inhibitors and pyroptosis inhibitors significantly improved the animal survival rate. Fourthly, they identified that p53 upregulation may lead to SLC7A11 and GPX4 downregulation, which can result in ferroptosis and trigger pyroptosis. Finally, they demonstrated that SIRT1-mediated p53/GPX4/GSDMD signaling pathway is dependent on p53 deacetylation, and inhibiting p53 and enhancing GPX4 in ALF model mice by drugs reduced AST and ALT and inflammatory reactions compared with results in the ALF model group. But The manuscript has several weaknesses. Firstly, the authors did not investigate the role of other pathways in ALF. Secondly, the sample size was relatively small, and the results may not be generalizable to a larger population. Thirdly, the authors did not discuss the potential risks of using drugs to inhibit p53 and enhance

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GPX4 in ALF model mice. Fourthly, the authors did not provide any evidence for the clinical relevance of their findings. Finally, the authors did not provide any information on the long-term effects of pre-treatment with ferroptosis inhibitors and pyroptosis inhibitors.

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Peer-review model: Single blind

Reviewer's code: 06373083
Position: Peer Reviewer
Academic degree: MD
Professional title: Doctor
Reviewer's Country/Territory: United States
Author's Country/Territory: China

Manuscript submission date: 2023-10-05

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2023-11-30 03:44

Reviewer performed review: 2023-11-30 13:37

Review time: 9 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Original Findings: Original Findings: The manuscript effectively elucidates the role of SIRT1 in ameliorating hepatocyte death in acute liver failure by targeting ferroptosis and pyroptosis through the p53/GPX4/GSDMD axis. The identification of SIRT1's dual regulation in mitigating both pathways is a novel contribution. New Hypotheses and Phenomena: The study proposes a novel therapeutic approach by activating SIRT1 to reduce hepatocyte death. The experimental evidence convincingly supports the hypothesis that SIRT1 intervention can modulate the p53/GPX4/GSDMD axis, highlighting new phenomena in the context of acute liver failure. Confirmed Hypotheses: The study confirms the hypothesis that SIRT1 activation reduces ferroptosis and pyroptosis, offering a mechanistic understanding of how SIRT1 exerts its protective effects in acute liver failure. Quality and Importance: Quality of Manuscript: The manuscript demonstrates high quality in experimental design, methods, and data analysis. The clarity of presentation could be improved for better comprehension. New Findings and Concepts: The study introduces a novel therapeutic target (SIRT1) in the context of acute liver failure, emphasizing its importance. The identification of the

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p53/GPX4/GSDMD axis as a key regulatory pathway adds a new conceptual dimension to our understanding. New Methods: While the study mainly focuses on experimental approaches, consider discussing any innovative methods employed in elucidating the SIRT1-mediated regulation of ferroptosis and pyroptosis. Conclusion Appropriateness: The conclusions appropriately summarize the data provided, emphasizing SIRT1 as a potential therapeutic target and the involvement of the p53/GPX4/GSDMD axis. Unique Insights: The study provides unique insights into the dual role of SIRT1 in regulating ferroptosis and pyroptosis, setting it apart from existing literature. Key Problems Solved: The manuscript addresses a key problem in acute liver failure by unraveling the molecular mechanisms underlying hepatocyte death and proposing a targeted intervention. Limitations and Future Directions: Limitations: Acknowledge the limitations, such as the reliance on cellular and mouse models. Discuss the potential challenges in translating findings to human pathology. Future Directions: Clearly outline future directions, emphasizing the need for clinical correlation, validation in human samples, and exploration of additional contributing factors to hepatocyte death. Unsolved Questions/Issues: Highlight any questions or issues that remain unanswered, encouraging further investigation. Next Steps for Authors: Suggest potential next steps for the authors, such as addressing the translational gap or exploring additional mechanisms involved in acute liver failure. Impact on Science and Clinical Practice: Impact on Basic Science: This study significantly contributes to basic science by deepening our understanding of the molecular mechanisms governing hepatocyte death in acute liver failure. Impact on Clinical Practice: The findings hold translational potential, suggesting a potential impact on clinical practice by proposing SIRT1 activation as a therapeutic strategy. However, the translation to clinical settings needs careful consideration. Overall, the manuscript offers valuable insights, and addressing the outlined points will enhance its quality and impact in the field of acute liver failure

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Reviewer's code: 06400386
Position: Peer Reviewer
Academic degree: MD
Professional title: Doctor
Reviewer's Country/Territory: China
Author's Country/Territory: China

Manuscript submission date: 2023-10-05

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2023-11-30 02:13

Reviewer performed review: 2023-12-03 02:55

Review time: 3 Days

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Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The present manuscript investigated the function of SIRT1 on the amelioration of hepatocyte death by reducing ferroptosis and pyroptosis via p53/GPX4/GSDMD axis. The authors conducted extensive experiments to demonstrate activation of SIRT1 could attenuate LPS/D-GalN-induced ferroptosis and pyroptosis. The results are interesting, but the following issues need to be addressed: 1. The male GSDMD-/- mice is liver-specific knockout or systemic knockout? 2. The picture of the liver samples in Figure 2 seems to be treated, please provide the original images. From the H&E staining, how to see there are less structural damage in the pre-treatment of pifithrin-α or liproxstatin-1 and GSDMD-/- mice. 3. In the 3.2 section, the authors showed that "however, p53 mRNA levels in the liproxstatin-1 group were down-regulated (Figure 2D)", this result is listed in Figure 2G. Meanwhile, what do you want to say for this sentence? Moreover, the results of Figure 2G seems that it has not been described in the manuscript. 4. The knocked down or overexpression of one protein, the WB result needs to be provided to demonstrate that this protein is actually silenced or overexpressed.