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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48244

Title: High mobility group box-1 release from H2O2-injured hepatocytes due to sirt1 functional inhibition

Reviewer's code: 03766580

Reviewer's country: Greece

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-04-26 04:48

Reviewer performed review: 2019-04-26 04:51

Review time: 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[Y] Accept (General priority)	[Y] Anonymous
[Y] Grade C: Good	[Y] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[ ] General
			[Y] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

The present basic research study has been nicely designed and executed

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48244

Title: High mobility group box-1 release from H2O2-injured hepatocytes due to sirt1 functional inhibition

Reviewer's code: 03659753

Reviewer's country: Japan

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-04-26 11:10

Reviewer performed review: 2019-05-06 03:26

Review time: 9 Days and 16 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
[Y] Grade D: Fair	[ ] Grade D: Rejection	[Y] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

To authors The authors examined the relationship among parp1-sirt1-HMGB1 release and the mechanism of HMGB1 release from H2O2-injured hepatocytes related to sirt1 functional inhibition. I think this manuscript will be interesting and contain important

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information. However, some contents of the present study are unclear and so confusable. There are some problems as following: Major Comments 1. In Figure 4 and 5, HMGB1 protein levels should be shown. In these Figures, the authors examined the relationships between Sirt1 expression and HMGB1 acetylation. However, I cannot accurately understand the relationships between HMGB1 and Sirt1 expression in each condition. In Figure 5A, HMGB1 expression will be increased by EX527 treatment. However, in Figure 5D, HMGB1 expression is not different in any conditions, and only HMGB1 acetylation is increased by sh-Sirt1. Moreover, I cannot confirm the decrease of Sirt1 expression in H2O2 treatment, such as in Figure4A. These points should be explained more clearly. 2. In the last paragraph in Results section, the authors concluded that Sirt1 negatively regulated Parp1. However, the authors also mentioned "Parp1-Sirt1-HMGB1" pathway is crucial for HMGB1 acetylation and release. After all, what is the first alteration in H2O2 treatment? Is the acetylation of Parp1 or decrease of Sirt1 activity? These points are so important and should be shown correctly. 3. In the Introduction section, the authors hypothesize that "Sirt1 activity suppression leads to HMGB1 deacetylation" or "DNA damage triggers the cascade reaction of parp1–sirt1–HMGB1 deacetylation". However, this is inconsistent with your results in this study. 4. In Figure 2A, 2D, or 6A, the authors mentioned elevated LDH release, HMGB1 concentration, and NAD+ content are restored to nearly normal levels at 24 hr. However, why such results occur? At least the possible explanation should be mentioned in discussion section. Moreover, the data at 24hr should be added in Figure 6A. 5. The contents of Method section should be explained in more detail. For example, time course of H2O2 treatment should be described in Figure 2B, 2C, 6B, or 6C. In the immunoprecipitation assay, the control samples such as IP by IgG should be shown. For examples, in Figure 1E, it is so confusable that the protein level is different between IB Parp1 in IP Parp1 samples and Parp1. Images in Figure 1C or 3A should be shown in high magnification, because I

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cannot confirm the alterations. 6. In "H2O2-induced SIRT1 decrease leading to HMGB1 release" paragraph of Results section, the contents of manuscript and Figures are different. They should be corrected. 7. There will be many description errors. English proofreading should be carefully performed again.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48244

Title: High mobility group box-1 release from H2O2-injured hepatocytes due to sirt1 functional inhibition

Reviewer's code: 00646291

Reviewer's country: United Kingdom

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-04-26 05:43

Reviewer performed review: 2019-05-06 09:57

Review time: 10 Days and 4 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

"HMGB1 acts outside the cell as a damage-associated molecular pattern (DAMP) molecule, triggering the sterile inflammatory response which then becomes amplified by cytokines and chemokines." The sentence is not clear and should be rewritten. What is

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sterile inflammatory response? "In the present study, we hypothesize that HMGB1 release in H2O2-injured hepatocytes is regulated by DNA-damage-mediated parp1 activation, which causes NAD+ over-depletion followed by sirt1 activity suppression, leading to HMGB1 deacetylation and finally release." If SIRT1 activity is suppressed HMGB1 should be hypeacetylated and not deacetylated. Further details for the HMGB1 in the culture medium should be provided. In figure 1F increased Parp1 mRNA levels are shown in HFD/etOH treated mice, whereas the Parp1 protein levels seem to be the same in both control and HFD/etOH treated mice. Authors should discuss this discrepancy. "Together, these findings suggest that cultured hepatocytes are injured by H2O2 as a consequence of HMGB1 translocation from the nucleus to the cytoplasm and then released to medium with the concomitantly elevated proportion of the acetylated form." This conclusion should be rewritten as the results shown in the figure 3 do not suggest that hepatocytes are injured by H2O2 as a consequence of HMGB1 translocation from the nucleus to the cytoplasm. The only conclusion that can be derived from the results shown in figure 3 is that hypeacetylation of HMGB1 coincides with cytoplasmic localization of this protein. "Furthermore, the sirt1 enzyme activity in control group was 3.28±0.14 nmoL/mg/min, but was 3.06±0.13 nmoL/mg/min, 3.12±0.02 nmoL/mg/min and 085±0.05 nmoL/mg/min in H2O2 treated groups respectively (Fig4C)." Figure 4C does not show sirt1 enzymatic activity. "Cells were treated with 0.1 M SRT1720 (an activator of sirt1) for 4h, the HMGB1 contents in medium significantly decreased to 15.6±2.87ng/mL compared with 61.09±9.86 ng/mL in H2O2 treatment alone (Fig4D). Figure 4D does not show HMGB1 content in the medium. In the figure 5A the total HMGB1 protein levels increase in EX527 cells and not only the hyperacetylated HMGB1 protein levels. What is the reason for that Sirt1 protein levels decrease in cells treated with EX527? "The NAD+ levels decreased from 0.5h and reached ~50% inhibition at 8h, then restored 24h after cells

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were treated with H2O2 (Fig6A)." The 24h time point is not shown in figure 6A.

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