

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 84648

Title: Suberoylanilide hydroxamic acid upregulates reticulophagy receptor expression and promotes cell death in hepatocellular carcinoma cells

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06119421

Position: Peer Reviewer

Academic degree: N/A

Professional title: N/A

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

Manuscript submission date: 2023-03-23

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-04-13 10:04

Reviewer performed review: 2023-04-17 09:04

Review time: 3 Days and 23 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

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

SPECIFIC COMMENTS TO AUTHORS

The manuscript "Suberoylanilide hydroxamic acid upregulates reticulophagy receptor expression and promotes cell death in hepatocellular carcinoma cells" is focused on a novel therapeutic approach against hepatocellular carcinoma involving epigenetic modulators. In detail, the authors describe the relationship between FAM134B-induced reticulophagy and SAHA-mediated cell death through the analyses of viability, apoptosis, cell cycle, migration, and invasion of SAHA-treated Huh7 and MHCC97L cells. In addition, proteins related to the reticulophagy pathway, intrinsic mitochondrial apoptosis, and histone acetylation were quantified using western blotting, and Chromatin immunoprecipitation (ChIP) was used to verify H4K16 acetylation in the FAM134B promoter region. Endoplasmic reticulum (ER) and lysosome co-localization, and mitochondrial Ca²⁺ levels were characterized via confocal microscopy. The experimental section is well conducted and results excellently reported. My suggestion is to deepen the introduction section, in particular in the context of epigenetic regulation and hepatocellular carcinoma. What is already known? Please refer to these two review articles that described this aspect: 1. Chianese A, Santella B, Ambrosino A, Stelitano D,

Rinaldi L, Galdiero M, Zannella C, Franci G. Oncolytic Viruses in Combination Therapeutic Approaches with Epigenetic Modulators: Past, Present, and Future Perspectives. *Cancers (Basel)*. 2021 Jun 2;13(11):2761. doi: 10.3390/cancers13112761; 2. Zhao P, Malik S, Xing S. Epigenetic Mechanisms Involved in HCV-Induced Hepatocellular Carcinoma (HCC). *Front Oncol*. 2021 Jul 15;11:677926. doi: 10.3389/fonc.2021.677926. After this improvment, the article is suitable for publication.

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Peer-review model: Single blind

Reviewer's code: 05575380

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

Manuscript submission date: 2023-03-23

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-06-05 10:12

Reviewer performed review: 2023-06-05 10:15

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

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

SPECIFIC COMMENTS TO AUTHORS

Dear Editor, thank you so much for inviting me to revise this manuscript about HCC. This study addresses a current topic. The manuscript is quite well written and organized. English could be improved. Figures and tables are comprehensive and clear. The introduction explains in a clear and coherent manner the background of this study. We suggest the following modifications:

- Introduction section: although the authors correctly included important papers in this setting, we believe the evolving systemic treatment scenario for HCC should be further discussed and some recently published papers added within the introduction (PMID: 33820447; PMID: 34798793; PMID: 36633661; PMID: 35403533), only for a matter of consistency. We think it might be useful to introduce the topic of this interesting study.
- Methods and Statistical Analysis: nothing to add.
- Discussion section: Very interesting and timely discussion. Of note, the authors should expand the Discussion section, including a more personal perspective to reflect on. For example, they could answer the following questions – in order to facilitate the understanding of this complex topic to readers: what potential does this study hold? What are the knowledge gaps and how do researchers tackle them? How do you see this



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area unfolding in the next 5 years? We think it would be extremely interesting for the readers. However, we think the authors should be acknowledged for their work. In fact, they correctly addressed an important topic in HCC, the methods sound good and their discussion is well balanced. One additional little flaw: the authors could better explain the limitations of their work, in the last part of the Discussion. We believe this article is suitable for publication in the journal although some revisions are needed. The main strengths of this paper are that it addresses an interesting and very timely question and provides a clear answer, with some limitations. We suggest a linguistic revision and the addition of some references for a matter of consistency. Moreover, the authors should better clarify some points.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

Manuscript submission date: 2023-03-23

Reviewer chosen by: Jing-Jie Wang

Reviewer accepted review: 2023-07-17 18:17

Reviewer performed review: 2023-07-17 18:18

Review time: 1 Hour

Scientific quality	[<input checked="" type="radio"/>] Grade A: Excellent [<input type="radio"/>] Grade B: Very good [<input type="radio"/>] Grade C: Good [<input type="radio"/>] Grade D: Fair [<input type="radio"/>] Grade E: Do not publish
Language quality	[<input checked="" type="radio"/>] Grade A: Priority publishing [<input type="radio"/>] Grade B: Minor language polishing [<input type="radio"/>] Grade C: A great deal of language polishing [<input type="radio"/>] Grade D: Rejection
Conclusion	[<input checked="" type="radio"/>] Accept (High priority) [<input type="radio"/>] Accept (General priority) [<input type="radio"/>] Minor revision [<input type="radio"/>] Major revision [<input type="radio"/>] Rejection
Peer-reviewer	Peer-Review: [<input checked="" type="radio"/>] Anonymous [<input type="radio"/>] Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

acceptance.