Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: office@baishideng.com
https://www.wjgnet.com

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 89738

Title: ALKBH5 suppresses autophagy flux via m6A demethylation of ZKSCAN3 mRNA in acute pancreatitis

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05401770
Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Assistant Professor, Doctor, Senior Researcher, Senior Scientist
Reviewer's Country/Territory: Iran
Author's Country/Territory: China

Manuscript submission date: 2023-11-11
Reviewer chosen by: Jia-Ru Fan
Reviewer accepted review: 2024-01-15 10:38
Reviewer performed review: 2024-01-20 08:46
Review time: 4 Days and 22 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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish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

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: office@baishideng.com
https://www.wjgnet.com

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) [ ] Minor revision [Y] 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

Please refere to the attached manuscript.

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: office@baishideng.com
https://www.wjgnet.com

Questions and Answers

Dear Reviewer:

We extend our warmest wishes to you for Chinese Lunar New Year of the Dragon! We sincerely appreciate your dedication in taking the time, amidst your busy schedule, to review our manuscript. Your insightful suggestions are truly valuable. After a thorough examination of the manuscript, we have wholeheartedly embraced your recommendations and made meticulous revisions accordingly.

Reviewer 1

Q1: In the main text of the article, method, result and discussion should come after the introduction.

A1: In accordance with your valuable suggestion and after carefully reviewing the requirements of the journal, we have adjusted the paragraph sequence. Currently, the main text of the paper strictly follows the order of introduction, methods, results, and discussion.

Q2: In this section, give incidence and prevalence of acute pancreatitis.

A2: Thank you for your valuable suggestions! We have carefully reviewed the relevant literature. We have added the content to the original text.

"The global prevalence and incidence of AP are approximately 76/100000 and 34/100000, respectively, and the number of new cases is increasing at an annual rate of 3%."

Reference:

[1] Iannuzzi JP, King JA, Leong JH, Quan J, Windsor JW, Tanyingoh D, Coward S,

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: office@baishideng.com
https://www.wjgnet.com

Forbes N, Heitman SJ, Shaheen AA, Swain M, Buie M, Underwood FE, Kaplan GG. Global Incidence of Acute Pancreatitis Is Increasing Over Time: A Systematic Review and Meta-Analysis. Gastroenterology 2022; 162(1): 122-134 [PMID: 34571026 DOI: 10.1053/j.gastro.2021.09.043]

[2] Mederos MA, Reber HA, Girgis MD. Acute Pancreatitis: A Review. Jama 2021; 325(4): 382-390 [PMID: 33496779 DOI: 10.1001/jama.2020.20317]

[3] Ouyang G, Pan G, Liu Q, Wu Y, Liu Z, Lu W, Li S, Zhou Z, Wen Y. The global, regional, and national burden of pancreatitis in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. BMC Med 2020; 18(1): 388 [PMID: 33298026 DOI: 10.1186/s12916-020-01859-5]

Q3: What studies?? Only one reference study is given.

A3: Thanks for thoroughly reviewing our manuscript! We have recognized this error. We have consulted relevant literature and added references to the original text. These references are review articles summarizing multiple studies, providing a detailed overview of the role of impaired autophagy in various diseases.

Reference:

[1] Mizushima N, Levine B. Autophagy in Human Diseases. N Engl J Med 2020; 383(16): 1564-1576 [PMID: 33053285 DOI: 10.1056/NEJMra2022774]

[2] Klionsky DJ, Petroni G, Amaravadi RK, Baehrecke EH, Ballabio A, Boya P, Bravo-San Pedro JM, Cadwell K, Cecconi F, Choi AMK, Choi ME, Chu CT, Codogno P, Colombo MI, Cuervo AM, Deretic V, Dikic I, Elazar Z, Eskelinen EL, Fimia GM, Gewirtz DA, Green DR, Hansen M, Jäättelä M, Johansen T, Juhász G, Karantza V, Kraft C, Kroemer G, Ktistakis NT, Kumar S, Lopez-Otin C, Macleod KF, Madeo F, Martinez J, Meléndez A, Mizushima N, Münz C, Penninger JM, Perera RM, Piacentini M, Reggiori F, Rubinsztein DC, Ryan KM, Sadoshima J, Santambrogio L,

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: office@baishideng.com
https://www.wjgnet.com

Scorrano L, Simon HU, Simon AK, Simonsen A, Stolz A, Tavernarakis N, Tooze SA, Yoshimori T, Yuan J, Yue Z, Zhong Q, Galluzzi L, Pietrocola F. Autophagy in major human diseases. Embo j 2021; 40(19): e108863 [PMID: 34459017 DOI: 10.15252/embj.2021108863]

[3] Chen T, Tu S, Ding L, Jin M, Chen H, Zhou H. The role of autophagy in viral infections. J Biomed Sci 2023; 30(1): 5 [PMID: 36653801 DOI: 10.1186/s12929-023-00899-2]

Q4: Reference??

A4: Following your valuable suggestions, we have inserted a reference into the original text after reviewing the literature.

Reference:

[1] Yuan X, Wu J, Guo X, Li W, Luo C, Li S, Wang B, Tang L, Sun H. Autophagy in Acute Pancreatitis: Organelle Interaction and microRNA Regulation. Oxid Med Cell Longev 2021; 2021: 8811935 [PMID: 33628384 DOI: 10.1155/2021/8811935]

Q5: What studies?? Only one reference study is given.

A5: Thanks for your meticulous review. The first reference is an original research paper confirming that ZKSCAN3 is a key inhibitor of autophagy. The second reference is a review article that provides a detailed overview of the role and mechanisms of ZKSCAN3 in autophagy across various diseases.

Reference:

[1] Chauhan S, Goodwin JG, Chauhan S, Manyam G, Wang J, Kamat AM, Boyd DD. ZKSCAN3 is a master transcriptional repressor of autophagy. Mol Cell 2013; 50(1): 16-28 [PMID: 23434374 DOI: 10.1016/j.molcel.2013.01.024]

[2] Pan H, Yan Y, Liu C, Finkel T. The role of ZKSCAN3 in the transcriptional

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: office@baishideng.com
https://www.wjgnet.com

regulation of autophagy. Autophagy 2017; 13(7): 1235-1238 [PMID: 28581889 DOI: 10.1080/15548627.2017.1320635]

Q6: Reference??

A6: Thanks for your valuable suggestions. We have consulted PubMed, Web of Science and various databases, and found no related study about ZKSCAN3's role in autophagy of acute pancreatitis. Therefore, here is no reference, and this is the purpose of our research.

Q7: Although ALKBH5 is one of the key words of this research, there are limited studies in the introduction?!

A7: Thank you for your suggestion, we have added relevant contents to the original text.

"ALKBH5 is a crucial demethylase that plays a key role in various diseases[19, 20]. In ovarian cancer, the overexpression of ALKBH5 promotes the formation of the BCL-2-Beclin1 complex, and inhibits autophagy [21]. In silica-related pneumonia, ALKBH5 can mediate autophagic flux blockade through the Slam7 pathway [22]. However, in myocardial ischemia-reperfusion injury, ALKBH5 plays a role in promoting autophagic flux [23]."

Q8: This section is related to the results part and to some extent the discussion and conclusion part, but it is mentioned in the introduction part.

Q9: In this part, the importance and necessity of doing this research should be mentioned.

A8 and A9: Thanks for your corrections. We have rewritten this paragraph to reflect the importance and necessity of doing this research.

"Clarifying the regulatory mechanism of autophagy in AP is crucial for early

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: office@baishideng.com
https://www.wjgnet.com

intervention. However, research on the autophagy and its regulatory mechanism in AP has not been illustrated. Therefore, in this article we aimed to explore the role and mechanism of action of ALKBH5 in ZKSCAN3 regulated autophagy. We verified the results at the cellular level through a series of molecular biology experiments, which provided a novel perspective on the research of pathogenesis and molecular mechanism of AP and highlighted new targets for therapeutic intervention."

Q10: Full name should be used next to the abbreviation because it is the first time it appears in the text.

A10: Thanks for your suggestion. We have made the correction in the original text, replacing "WB" with "Western blot (WB)."

Q11: What clues?!

A11: Dear reviewer, following your suggestion, we have provided detailed explanations in the original text. The clue here means that the transcription factor ZKSCAN3 and the demethylase ALKBH5 play an important role in the occurrence and development of acute pancreatitis, which provides certain reference value for future in-depth exploration and early drug treatment.

Q12: Study setting and type of study should be explained in the details.

A12: According to your suggestion, we explained in the last paragraph of the introduction that we have conducted a series of molecular biology experiments at the cellular level and tested relevant genes at the mRNA and protein levels to verify our scientific questions.

Q13: The authors should include information about the availability of Ethical

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: office@baishideng.com
https://www.wjgnet.com

Permission to conduct the study. Also, in the method section, the authors should explain about the ethical issue.

A13: This study verified our scientific questions at the cellular level. The cells required for the experiments were all mature cell lines purchased by biological company. It did not involve stem cell, primary cell extraction, animal experiments, or clinical trials. Therefore, this study did not involve ethical issues. We will explain it in the ethical issues section of the article.

Sincerely yours,

Tao Zhang

Shuai Zhu

Geng-wen Huang