

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 77964

Title: Hypoxia inducible factor 1 α promotes interleukin-1 receptor antagonist expression during hepatic ischemia-reperfusion injury

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03475142

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: China

Manuscript submission date: 2022-05-30

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-06-23 06:33

Reviewer performed review: 2022-07-05 18:49

Review time: 12 Days and 12 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
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 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="radio"/>] Anonymous [<input type="radio"/>] Onymous
	Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript was reviewed for publication in the journal. The manuscript was designed to evaluate a mechanism that could protect the liver in the early stage of ischemia-reperfusion injury (IRI). The results obtained show that ischemia or hypoxia leads to increased expression of interleukin-1 receptor antagonist (IL-1ra) regulated by HIF-1alpha and that ischemic preconditioning (IP) protects the liver from IRI via the HIF-1alpha-IL-1ra pathway. It is the reviewer's opinion that the manuscript is interesting and easy to follow. However, it appears that there are a couple of concerns in the manuscript. 1) The authors should express the abbreviations of the words (e.g. IL-1ra, and IL1rn) in the abstract. 2) Figure 2B shows the protein levels of IL-1ra in the liver after IRI. How about the quantitative analysis? 3) Figure 2D shows the statistical analysis of immunohistochemical scores. In general, the score should be shown as a dot plot. Also, a specific statistical analysis should be considered. 4) Cells were subjected to hypoxia-reoxygenation (HR) in the study. The authors should express the detail condition of hypoxia. Did the authors confirm the hypoxia by measuring the concentration of oxygen level in the medium? 5) Figure 2D shows the protein levels of IL-1ra in AML12 cells after HR. How about the quantitative analysis? 6) Figure 4B and 4E show the protein levels of IL-1ra in the liver after ischemia and the protein levels of IL-1ra in AML12 cells after hypoxia. How about the quantitative analysis in both experiments? 7) Figure 5A, 5b and 5E also needs the quantitative analysis to confirm the results. 8) Figure 7I and 7J need much better images for the IL-1ra expression or the quantitative analysis for better understanding. 9) The authors analyzed the gene enrichment analysis for IR3h and IS 1.5h and IL1rn was focused. How about the gene



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enrichment analysis in different time point (e.g. IR6h)? 10) The authors showed that IP protected the liver by promoting IL-1ra expression via HIF-1alpha. The results appear to be already known?

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Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04410177

Position: Peer Reviewer

Academic degree: PhD

Professional title: Assistant Professor, Senior Statistician, Statistical Worker, Statistician

Reviewer's Country/Territory: Taiwan

Author's Country/Territory: China

Manuscript submission date: 2022-05-30

Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2022-07-18 16:26

Reviewer performed review: 2022-07-25 07:37

Review time: 6 Days and 15 Hours

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
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" 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 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="radio"/>] Anonymous [<input type="radio"/>] Onymous Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No
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SPECIFIC COMMENTS TO AUTHORS

This is a basic study discussing about whether there was the protective effect of IP is exerted precisely by the promotion of the accumulation of HIF-1 α and regulation of the expression of IL-1ra, leading to the inhibition of the IL-1 β signaling pathway and a reduction in hepatic IRI. This study results confirms through in vivo and in vitro model. I think the topic is important and contributive to the clinical practice with an empirical approach quite valuable for hepatic ischemia-reperfusion injury professionals. 1 Title: Appropriate. 2 Abstract: Well described in the manuscript. 3 Key words: Appropriate. 4 Background: Please add references about review article related to similar issue. 5 Methods: Appropriate. 6 Results: Appropriate. 7 Discussion: I am not familiar the hypothesis proposed in this study. The authors should clarify this concern for discussion. 8 Illustrations and tables: I am not familiar in vivo and in vitro model. Please introduce commonly used illustrations and tables for mediation model. 9 Biostatistics: Does the manuscript examined by experienced biostatistics? One-way analysis of variance (ANOVA) based on normal distribution assumption. 10 Units: Does the manuscript meet the requirements of use of international system of units? 11 References: Please cite appropriately the latest, important and authoritative references in the introduction and discussion sections. 12 Quality of manuscript organization and presentation: Please provide English editing certificate. 13 Research methods and reporting: Please provide appropriate research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial;

(3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. 14 Ethics statements: Please provide appropriate ethics approval.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Reviewer's code: 03475142

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: China

Manuscript submission date: 2022-05-30

Reviewer chosen by: Jing-Jie Wang

Reviewer accepted review: 2022-08-18 07:32

Reviewer performed review: 2022-08-19 02:37

Review time: 19 Hours

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
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 checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

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

SPECIFIC COMMENTS TO AUTHORS

The manuscript was re-reviewed for publication in the journal. The manuscript was designed to evaluate a mechanism that could protect the liver in the early stage of ischemia-reperfusion injury (IRI). The results obtained show that ischemia or hypoxia leads to increased expression of interleukin-1 receptor antagonist (IL-1ra) regulated by HIF-1alpha and that ischemic preconditioning (IP) protects the liver from IRI via the HIF-1alpha-IL-1ra pathway. It is the reviewer's opinion that the manuscript is interesting and easy to follow. The authors promptly explained/discussed all issues/points. I have no more concern in the manuscript.