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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 51464

Title: GSDMD-medicated hepatocyte pyroptosis expands inflammatory responses to aggravate acute liver failure by up-regulating MC Y/CCR2 to recruit macrophages

Reviewer's code: 03293832
Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Doctor
Reviewer's country: Japan
Author's country: China

Reviewer chosen by: Artificial Intelligence Technique
Reviewer accepted review: 2019-09-20 03:09
Reviewer performed review: 2019-09-26 05:04
Review time: 6 Days and 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[Y] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] 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[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

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The manuscript describes the involvement of GSDMD on hepatocyte pyroptosis in acute liver failure using AML12 mouse lined hepatocytes, genetically engineered mice, and human samples. They showed that GSDMD positively regulates recruited macrophages to release inflammatory mediators and to lead expansion of the secondary inflammatory responses. They suggest that inhibition of GSDMD can reduce hepatocyte death and the secondary inflammatory responses of acute liver failure. I, reviewer suggest that the manuscript deserves publication in WJG if following items are improved; 1. The results section in abstract should be more concretely showing the real data (numerical value) of pivotal points. 2. Introduction is too long. Make it neat and tidy. 3. Define 'healthy liver tissue'. Were they from part of deceased or living donor ? 4. Define 'Cell inhibition' shown in Figure 2. Describe in Materials and Methods. 5. Description in 'Statistical analysis' is messy. Should be revised by a person who knows statistics well.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

[ ] The same title

[ ] Duplicate publication

[ ] Plagiarism

[Y] No

BPG Search:

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[ ] Plagiarism

[Y] No

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 51464

Title: GSDMD-medicated hepatocyte pyroptosis expands inflammatory responses to aggravate acute liver failure by up-regulating MC Y/CCR2 to recruit macrophages

Reviewer's code: 02860897
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Associate Professor
Reviewer's country: Japan
Author's country: China
Reviewer chosen by: Jin-Zhou Tang
Reviewer accepted review: 2019-09-25 14:26
Reviewer performed review: 2019-09-27 14:08
Review time: 1 Day and 23 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) [Y] Minor revision [ ] 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

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Humans express a complex array of chemokines and chemokine receptors that collectively orchestrate the trafficking of leukocytes, a central feature of the innate immune response. CC chemokine receptor 2 (CCR2) is the major chemokine receptor on monocytes and macrophages, cells that play central roles in the pathology of atherosclerosis, obesity, and type 2 diabetes. In atherosclerosis, CCR2 activation by the monocyte chemoattractant proteins MCP-1, MCP-2, and MCP-3 induces the recruitment of monocytes from the blood into the arterial walls, where they differentiate into macrophages and contribute to the development of atherosclerotic plaques. In acute liver failure, CCR2 activation by MCP1 is associated with macrophage infiltration. As an executor of pyroptosis, GSDMD plays a key role in the pathogenesis of acute liver failure. Major 1.This mechanism of inflammation has also been proposed for other liver disease such as steatohepatitis. Does pyroptosis play an important role only in the early stages of acute liver failure? 2.Please clarify the role of MCP-2 and MCP-3.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 51464

Title: GSDMD-medicated hepatocyte pyroptosis expands inflammatory responses to aggravate acute liver failure by up-regulating MC Y/CCR2 to recruit macrophages

Reviewer's code: 03671246
Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Associate Professor
Reviewer's country: Thailand
Author's country: China
Reviewer chosen by: Artificial Intelligence Technique
Reviewer accepted review: 2019-09-26 07:52
Reviewer performed review: 2019-10-06 18:28
Review time: 10 Days and 10 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: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

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Major comments: 1. Please clarify the cell sources of MCP1/CCR2 in the manuscript. The author should probe the involvement of MCP1/CCR2 in GSDMD-mediated pyroptosis through blocking CCL2/CCR2 axis. 2. Fig. 3A should include the sample without transfection. 3. In Fig. 4A, GSDMD accounted for about 55% survival while wt had only 25% survival beyond 12 h post-treatment. These numerical figures extracted from the graph are not in agreement with "12/15" and "1/15" written on the graph. A rescue of 30% (55%-25%) was accountable by GSDMD-mediated pyroptosis. What was responsible for the remaining 45% death? Were they caused by necrosis / apoptosis? 4. In Fig. 5A, GSDMD-N almost virtually disappeared. This is not in agreement with 70% efficiency of shRNA against GSDMD shown in Fig. 3A. Minor comments: 1. "GSDMD-medicated" in the title and throughout the manuscript should be corrected as "GSDMD-mediated". 2. How to calculate cell inhibition rate? 3. The labels in most bar graphs are too small and illegible.

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