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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47869

Title: Honokiol-enhanced cytotoxic T lymphocyte activity against cholangiocarcinoma cells mediated by dendritic cells pulsed with damage-associated molecular pattern

Reviewer's code: 00057659

Reviewer's country: Germany

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-03-29 07:23

Reviewer performed review: 2019-03-29 08:02

Review time: 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[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

Honokiol was shown to positively influence the immune system in different settings. Especially the action against Tumors (lung, breast, hepatocellular) makes this compound interesting. For the first time, the action of honokiol on cholangiocellular carcinoma was

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investigated. The authors could show with appropriate methods a positive influence of the drug also in this setting.

INITIAL REVIEW OF THE MANUSCRIPT

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[ ] Plagiarism

[Y] No

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47869

Title: Honokiol-enhanced cytotoxic T lymphocyte activity against cholangiocarcinoma cells mediated by dendritic cells pulsed with damage-associated molecular pattern

Reviewer's code: 00291404

Reviewer's country: United States

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-14 11:25

Reviewer performed review: 2019-05-15 13:33

Review time: 1 Day and 2 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High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

There are some major issues with this study. 1. The authors have used one human cancer cell line (KKU-213L5 cells) as the only target cells of study, and then some DCs and T lymphocytes from healthy donors. In both case, HLA types are unknown. The authors

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forget the very basic knowledge that for adaptive antitumor immunity, matched HLA types of immune cells and cancer cells are needed in order to elicit adaptive immune responses and mediate specific targeted cancer cell killing. From the data presented in Figure 6, it is so obvious that the cytotoxic effect was minimal, HLA-independent and non-specific. Therefore, the authors have to find some donors who match the HLA types of the target cells KKU-213L5 cells and re-do the whole experiments in Figure 6 with right controls. 2. The study on immunogenic cell death. There are two types of signals derived from DAMPs (and PAMPs). One is called "find-me" signal, such as extracellular ATP and HMGB1; and the second type is called "eat-me" signal, such as ecto-CRT (calreticulin) now expressed on the cell surface. The ecto-expression of CRT and other HSPs on the cell surface send the signal to phagocytes to "eat me". Therefore, the data presented in Figure 1D consist of find-me signals only. It is equally important to analyze the cell surface expression of DAMPs such as ecto-CRT. Please see, Kepp O et al., Consensus guidelines for the detection of immunogenic cell death. Oncoimmunology. 2014; 3:e955691. [PMID: 25941621] 3. The effect of honokiol on cancer cells have been quite well studied. Some have studied how honokiol modulates cancer immunogenicity, and the authors have missed referring to them. For example, (1). Liu SH. Et al., Honokiol confers immunogenicity by dictating calreticulin exposure, activating ER stress and inhibiting epithelial-to-mesenchymal transition. Mol Oncol. 2015; 9(4):834-49. (2). Lin CJ et al., Honokiol induces autophagic cell death in malignant glioma through reactive oxygen species-mediated regulation of the p53/PI3K/Akt/mTOR signaling pathway. Toxicol Appl Pharmacol. 2016; 304:59-69. (3). Li L, Han W, Gu Y, Qiu S, Lu Q, Jin J, Luo J, Hu X. Honokiol induces a necrotic cell death through the mitochondrial permeability transition pore. Cancer Res. 2007; 67:4894-903. Other minor issues are, 1. The title. "...pulsed with DAMP components-derived tumor cell lysates". The phrase is a bit weird and I do not

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understand what the authors try to say. 2. Figure 4. The data were presented as mean +/- SEM. In fact, with so few data points, the right way to present the data is mean +/- SD. 3. In all figure legends, it should be "p value", not some other symbol. 4. Page 13. "DCs pulsed with tumor cell lysates derived from honokiol-treated CCA cells induced T lymphocyte production of cytokines". From the subtitle, the authors implied that IFN-gamma and IL-12 were all produced from T lymphocytes in the co-culture. This may not be true as DCs can produce these cytokines. Please modify the statement.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

[ ] The same title

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[Y] No

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47869

Title: Honokiol-enhanced cytotoxic T lymphocyte activity against cholangiocarcinoma cells mediated by dendritic cells pulsed with damage-associated molecular pattern

Reviewer's code: 02739495

Reviewer's country: China

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-20 01:01

Reviewer performed review: 2019-05-24 00:47

Review time: 3 Days 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

SPECIFIC COMMENTS TO AUTHORS

In this paper, Jiraviriyakul A et al. found that DCs loaded with cell lysates derived from honokiol-treated tumor cells enhance efficacy against cholangiocarcinoma. DCs pulsed with honokiol-derived tumor cell lysates can induce T lymphocyte proliferation and

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enhance killing of cholangiocarcinoma cells compared to DCs and DCs pulsed only with tumor cell lysate cell lysates. Here are suggestions for this article: 1. This article validates the tumoricidal cell function of DCs plus Honokiol-derived cell lysates. These results indicate changes in cell phenotype, but no relevant mechanisms have been studied. 2. In the results section of the paper, the model in this paper was derived from mononuclear cells that were mature DCs, why immature DCs were selected instead of mature DCs for co-localization with tumor cell lysates?

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47869

Title: Honokiol-enhanced cytotoxic T lymphocyte activity against cholangiocarcinoma cells mediated by dendritic cells pulsed with damage-associated molecular pattern

Reviewer's code: 00681914

Reviewer's country: Slovakia

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-22 13:29

Reviewer performed review: 2019-05-27 17:05

Review time: 5 Days and 3 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) [Y] Accept (General priority) [ ] Minor revision [ ] 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

SPECIFIC COMMENTS TO AUTHORS

The conclusions and novel findings are well stated and the essential data appropriately summarized The authors could better explain the future directions of the topic described. The impact for clinical practice is clearly shown.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47869

Title: Honokiol-enhanced cytotoxic T lymphocyte activity against cholangiocarcinoma cells mediated by dendritic cells pulsed with damage-associated molecular pattern

Reviewer's code: 03291363

Reviewer's country: Australia

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-16 11:45

Reviewer performed review: 2019-05-30 06:22

Review time: 13 Days and 18 Hours

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	[ ] 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	[Y] 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

The authors have investigated the ability of holokiol primed dendritic cells to increase killing of an invitro cholangiocarcinoma line: a very interesting study My comments: 1. The results section has a lot of methods in it: they should be redirected to the methods

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and the results section should simply state the results without interpretation 2. Tables are required to define the data that were used to generate Figures 5 and 6 3. The significant effect of addition of honokiol to DC pulsing is derived from 3 experiments at 48/24: this is not enough and the number need to be increased considerably 4. Is the killing effect seen in Figure 6 simply due to free holokiol and not its presence in pulsed Dc? Please explain?

INITIAL REVIEW OF THE MANUSCRIPT

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