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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 6634
Title: Naofen promotes TNF-α-mediated apoptosis of hepatocytes by activating caspase-3 in lipopolysaccharide-treated rats.
Reviewer code: 00462396
Science editor: Ma, Ya-Juan
Date sent for review: 2013-10-26 12:36
Date reviewed: 2013-10-30 18:43

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[Y] Grade C: a great deal of language polishing	[ ] No records	[Y]Rejection
[Y] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
Although this is a quite logic follow-up study of previous published research by the authors, the relevance of this study is not completely clear. The contribution of this article to the elucidation of the 'pathway' under investigation is questionable. More elaborated insight of parameters/cytokines/… that contribute to the induction of apoptosis induced by lipopolysaccharide must be provided. In addition, this paper assumes that apoptosis is the only mechanism of cell death. By only considering the latter, one can not exclude the role of other modes of cell death, in particular necrosis, which could also have an impact in the setting addressed by the authors. The authors must demonstrate that other types of cell death can be excluded prior to assuming that only apoptosis occurs. Furthermore, the methodology used is not explained clear enough. For example, the number of biological and technical repeats, and independent experiments, the number of rats per group, … are lacking.

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 6634
Title: Naofen promotes TNF-α-mediated apoptosis of hepatocytes by activating caspase-3 in lipopolysaccharide-treated rats.
Reviewer code: 00058872
Science editor: Ma, Ya-Juan
Date sent for review: 2013-10-26 12:36
Date reviewed: 2013-11-16 20:21

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[Y] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
The role of the spleen in inducing liver damage should be pinpoint. In fact, in the discussion section, Authors state that .....whereas our finding verified that the increase in naofen induced by LPS was limited in the liver, but not in the kidney, thymus or spleen (data not shown), indicating that naofen, in the action of LPS, may only have limited contribution to liver injury.....I would expected further comment on the role of the spleen in the liver diseases, obviously non cirrhotic. Authors are kindly requested to emphasise this point and quote the following papers: About the role of the spleen in NAFLD.....the recent pandemia! Could inflammatory markers help diagnose nonalcoholic steatohepatitis? Eur J Gastroenterol Hepatol. 2009 May;21(5):504-11. doi: 10.1097/MEG.0b013e3283229b40. Hepatic steatosis in overweight/obese females: new screening method for those at risk. World J Gastroenterol. 2009 Dec 7;15(45):5693-9. PMID: 19960566 [PubMed - indexed for MEDLINE] Free PMC Article Related citations About the role of the spleen. Spleen: A new role for an old player? World J Gastroenterol. 2011 Sep 7;17(33):3776-84. doi: 10.3748/wjg.v17.i33.3776. Review. Liver-spleen axis: intersection between immunity, infections and metabolism.. World J Gastroenterol. 2013 Jun 21;19(23):3534-42. doi: 10.3748/wjg.v19.i23.3534. PMID: 23801854 [PubMed - in process] Free PMC Article About the role of antiapoptotic imbalance Serum Bcl-2 concentrations in overweight-obese subjects with nonalcoholic fatty liver disease.. World J Gastroenterol. 2011 Dec 28;17(48):5280-8. doi: 10.3748/wjg.v17.i48.5280. PMID: 22219597 [PubMed - indexed for MEDLINE] Free PMC Article About the so-called liver-spleen axis Liver-spleen axis, insulin-like growth factor-(IGF)-I axis and fat mass in overweight/obese females. J Transl Med. 2011 Aug 16;9:136. doi: 10.1186/1479-5876-9-136.

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 6634
Title: Naofen promotes TNF-α-mediated apoptosis of hepatocytes by activating caspase-3 in lipopolysaccharide-treated rats.
Reviewer code: 02638641
Science editor: Ma, Ya-Juan
Date sent for review: 2013-10-26 12:36
Date reviewed: 2013-11-18 16:38

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[Y] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[Y] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
The article investigated the role of naofen in TNF-α-mediated apoptosis of hepatocytes induced by LPS. It was concluded that TNF-α released from KCs treated with LPS may induce hepatic naofen expression and then stimulate hepatocellular apoptosis through activation of caspase-3. The study is novel and well designed. However, there are several points to be figured out. 1. As it was described in the manuscript that treatment with TNF-α alone did not cause the apoptosis of primary hepatocytes, the conclusion of the manuscript should be carefully reconsidered. 2. If KCs treated with LPS stimulated hepatocellular apoptosis via TNF-naofen pathway,the inhibitors to block naofen expression should be used in the study to confirm the conclusion. 3. In the introduction part, more background information about naofen should be mentioned to emphasize the aim or rationale of the study. 4. How many times were repeated in the vitro experiments using primary hepatocytes or KCs. It should be mentioned in the manuscript. 5. Had the TUNEL staining and Western blotting been quantitatively analyzed?

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 6634
Title: Naofen promotes TNF-α-mediated apoptosis of hepatocytes by activating caspase-3 in lipopolysaccharide-treated rats.
Reviewer code: 00503458
Science editor: Ma, Ya-Juan
Date sent for review: 2013-10-26 12:36
Date reviewed: 2013-11-29 21:10

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[Y] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
In this manuscript the authors investigated the role of naofen in TNF-?-mediated apoptosis of hepatocytes induced by LPS. They found that LPS injection significantly induce both TNF-? and naofen expression as well as caspase-3 activity and, this effect is prevented by pre-treatment with anti-TNF-? antibody. Moreover, they demonstrated that this observation cannot be reproduced in hepatocytes neither by TNF-? alone or LPS alone, whereas the incubation of hepatocytes with conditioned culture medium of Kuppfer cells (KC-CM) treated with LPS induce both naofen expression and caspase-3 activation. Thus, the authors conclude that TNF-? released by KCs treated with LPS may induced the expression of naofen in hepatocytes which in turn induced apoptosis through activation of caspase-3. In a previous study the authors have shown that TNF-?-mediated increase of naofen expression induced activation of caspase-3, resulting in apoptosis in human embryonic kidney (HEK) 293 cells. Moreover, in a recent paper the same authors demonstrated that intravenous injections of LPS enhanced the expression of naofen and caspase-3 activity in rat livers. Even in this study the authors showed that in isolated KCs or hepatocytes, LPS hardly affected naofen expression and caspase-3 activity, whereas incubation of hepatocytes with KC-CM enhanced both naofen expression and caspase-3 activation. Thus, the authors concluded that LPS may induce the hepatic apoptosis in association with enhanced naofen expression, and that naofen may mediate the activation of caspase-3. Due to the previous studies already published by the authors the novelty of the present manuscript is significantly reduced and most of the experiments are overlapping thus, the authors should deeply investigate the molecular mechanism through which TNF-??induce expression of naofen in rat liver and which other factors of the KC-CM contribute to induction of

apoptosis.