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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 23771
Title: Adult mouse model of early hepatocellular carcinoma promoted by alcoholic liver disease
Reviewer's code: 01560575
Reviewer's country: Japan
Science editor: Ze-Mao Gong
Date sent for review: 2015-12-17 14:58
Date reviewed: 2015-12-24 07:59

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Major comments The fact is that this manuscript tries to demonstrate the accelerating effect of ethanol in chemo-carcinogenesis by DEN and that this mouse model does not essentially represent the model of hepato-carcinogenesis induced by chronic ethanol consumption, namely the hepatocellular carcinoma seen in alcoholic cirrhosis, even if the histopathological features would resemble those of alcoholic hepatitis, fibrosis or cirrhosis. The authors should always be aware of this fact whenever they write sentences since there are many confusions some of which are critical and should be omitted some of which are listed below. Otherwise, this manuscript is well written. Minor comments 1. Page 18, lines 15. "By utilizing adult mice and the Lieber-DeCarli alcohol diet, our model displays the natural course and progression of alcoholic liver disease and shows acceleration of early hepatobiliary tumors after a chemical carcinogen exposure" should be changed to, "By utilizing adult mice and the Lieber-DeCarli alcohol diet, our model shows acceleration of early hepatobiliary tumors after a chemical carcinogen exposure with some histopathological resemblance to human alcoholic liver diseases". The natural course and progression of alcoholic liver disease takes

about 6 years even in baboons fed Lieber-DeCarli diet that was proven by Lieber et al. 2. Page 22, lines 22. The sentence, "Our model involves a sequencial step-wise progression of alcoholic liver disease to HCC" should be omitted. 3. Page 23, line 1. "This combination of carcinogen pre-exposure and chronic alcohol consumption presents one of the most unique phenomenons of chronic alcohol leading to progression of HCC that occurs in humans", should be omitted.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 23771
Title: Adult mouse model of early hepatocellular carcinoma promoted by alcoholic liver disease
Reviewer's code: 00004603
Reviewer's country: United States
Science editor: Ze-Mao Gong
Date sent for review: 2015-12-17 14:58
Date reviewed: 2016-01-09 01:23

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
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[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This is an interesting manuscript devoted to increased DEN-induced HCC development by alcohol. An important aspect of this study is that mice were fed not ethanol in water, but ethanol in Lieber De Carli diet (pair-feeding), which by itself induces liver injury. There are couple of questions/suggestions to this study: 1. Although many chemical/histological parameters were determined, the design of the study does not allow distinguishing between the factors that drive HCC progression and those which accompany HCC development. However, more detailed pathogenic aspects are probably planned for future studies. 2. The progression to HCC is confirmed by MRI. Considerable attention is attracted to liver macrophages and neutrophils, which claimed to play a role in HCC pathogenesis, The negative side of these studies is the characterization of macrophages as M1 and M2, which both are activated and thus, it is not clear what it can add to understanding of the mechanisms of alcohol-shaped HCC development and why in Discussion alcohol-induced switch to only M2 phenotype is emphasized. 3. Since it is known that induction of oxidative stress and ER stress in hepatocytes leads to HCC development, it will be reasonable to

measure some parameters of oxidative stress is alcohol-fed mice exposed to DEN (like 4HNE-expression in hepatocytes, TBARS, glutathione levels). 4. It has been shown in the literature that liver steatosis, but not alcohol per se affects HCC development. Do you think that in your case the increased HCC induction by DEN in alcohol-fed mice is attributed to alcohol metabolism or it requires liver fat accumulation as a consequence of ethanol metabolism?