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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 15090
Title: Loss of Dicer1 impairs hepatocyte survival and leads to chronic inflammation and progenitor cells activation
Reviewer code: 02936191
Science editor: Yuan Qi
Date sent for review: 2014-11-08 21:35
Date reviewed: 2014-12-08 23:49

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	[ ] Existing	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair	[ ] Grade D: Rejected	BPG Search:	[ ] Rejection
[ ] Grade E: Poor		[ ] Existing	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

Authors generated a hepatocyte-selective Dicer1 knockout mouse and observed the gradual hepatic histopathological changes in the mutant liver, including hepatocyte proliferative and apoptosis, liver necrosis and inflammation, HCC development and so on. Although related work has been previously published, authors did great jobs on the further detail continuous hepatic histopathological processes in response to the loss of Dicer1. It's a good complement to the previous research. However, a minor language polishing is required.

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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Gastroenterology
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Title: Loss of Dicer1 impairs hepatocyte survival and leads to chronic inflammation and progenitor cells activation
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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	[ ] Existing	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] No records	
[Y] Grade D: Fair		BPG Search:	[ ] Rejection
[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Existing	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

MicroRNAs have important roles in liver biologies. Therefore it is important to examine their roles in liver development and diseases using animal models. It was previously reported that liver-specific Dicer1 knockout mice showed impaired lipid metabolism and eventually develop hepatocellular carcinoma. In this paper, the authors further characterized the gradual histological processes of spontaneous development of HCC. HCC development and defects in lipid metabolism have been already reported. Therefore, the novelty of this work is that they analyzed types of cells death as well as inflammation and fibrosis. However, the authors should provide clearer data to show necrosis, inflammation, and fibrosis and be more careful to discuss how fibrosis and HCC are developed in Dicer1-/- mice. Specific points. Fig. 1B is not clear. I could see Dicer1 band in the lane for Dicer1-/- at 4month. Clearer Western blot data should be provided to conclude that Dicer 1 could not be detected at all the time points. The authors described that in addition to apoptosis, hepatocyte necrosis could be observed in Dicer1-/- mice. How did the authors detected necrotic hepatocytes? Is it possible to provide a quantitative data for necrosis as the authors provided for TUNEL+ and Ki67+ cells in Fig. 3C? In Fig. 4, the authors described that inflammatory cells including neutrophils and eosinophils infiltrated into KO liver tissues. How did the authors know those infiltrated cells were neutrophils and eosinophils? They mentioned that CK19+ progenitor cells increased in KO mice (Fig. 5). However, in contrast to previous reports, proliferating CK19+ ductular cells were negative

for CD133- and OV6-. Since CD133 is expressed in normal bile ducts (Kamiya et al Gastroenterology 2009), it is weird that those CK19+ cells are negative for CD133. The authors should provide data of co-staining of CD133 and CK19 to show CK19+ proliferating ductular cells in Dicer1-/- mice are negative for CD133-. Do hepatocytes express OCT4 and SOX2 (Fig. 5B)? The authors should perform the staining of OCT4 or SOX2 with a hepatocyte marker such as HNF4? and C/EBP?. CK19 staining was performed at 2 and 4 months, whereas SOX2 and OCT4 staining was at 1 month. Why the authors performed those experiments at different stages? In Fig. 6A. why did the authors show Masson staining? It is hard to know whether there were fibrotic areas or not. Staining in panels in Fig. 6B are not clear. Did the authors try to show HCC are CK19+ or HNF4?+? Parts of HCC tissue were Dicer 1+ (Fig. 6C)? I could see brown area in the image at 12 month. Dicer1-/- tissues at 4 and 12 months slightly expressed Dicer1? (Fig. 6D) Page 9. The authors proved a data that 4 out of 20 mutant mice developed HCC. How about fibrosis? All the mutant mice developed liver fibrosis? In Discussion, the authors described that progenitor cells expand and become hepatocytes to compensate hepatocyte death. However, as the authors mentioned in Page 9 that hepatocytes expressed SOX2 and OCT4, suggesting hepatocytes, which escaped from apoptosis and necrosis, may alter their characteristics. Recent papers showed that progenitors do not majorly contribute to tissue repair by providing new hepatocytes (Yanger et al Genes and Dev. 2012, Tarlow et al Hepatology 2014). In addition, since the authors described that CK19+ cells were negative for CD133 and OV6, it is not clear whether those cells are liver progenitors or not. Therefore, the authors should carefully discuss how damaged liver tissue is compensated and how HCC is developed in Dicer1 KO mice. Other points. Page 8, the section “Dicer1-deficient mice develop chronic inflammation and fibrosis” What are “histocytes”? Page 9 KlF4 is probably KLF4. Fig. 6D Dicer1-/- means “non-tumor tissue”?

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ESPS PEER REVIEW REPORT

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
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[ ] Grade E: Poor		[ ] Existing	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

The article "Loss of Dicer1 impairs hepatocyte survival and leads to chronic inflammation and progenitor cells activation" by Lu et al., describes the generation of a hepatocyte-selective Dicer1 knockout mouse model and the investigation of the continuous hepatic histopathological processes in response to the loss of Dicer1 in this model. The results obtained in this study are interesting. The experiments have been done properly, and the interpretations of the data are mostly appropriate. Below are several specific comments : Fig 4B : There is no increase of serum IL-1β in the 2 months-old Dicer1-deficient mice. The authors should discuss about that. Fig 5B : There is no increase of Nanog expression the 2 months-old Dicer1-deficient mice. The authors should discuss about that. The authors should mention the Figure 6D in the text