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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 11644
Title: Deletion of CYLD increases resistance towards death-receptor mediated cell death in murine hepatocytes by triggering NF-κB signaling
Reviewer code: 00069015
Science editor: Ya-Juan Ma
Date sent for review: 2014-05-29 23:30
Date reviewed: 2014-06-05 21:06

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

COMMENTS TO AUTHORS

This study evaluated the CYLD's function in the murine hepatocytes apoptotisis network which controlled by NF-kB. The apoptosis related factors including Bcl-2, XIAP, cIAP and survivin were assessed after hepatocyte cell death in CYLD knockout mice. Subsequently, the study speculate CYLD regulate NF-kB dependent anti-apoptotic pathway. A excellent work had been done in this study. In terms of illuminate the hypothesis clearly, I recommend to make revisions: The study hypothesize CYLD locate in the center position of NF-kB dependent apoptosis pathway which related to many factors. In this situation, a graph is needed to illustrate this network. Apart from cell viability, western blot, had the flow cytometry analysis already been performed in CYLD(-/-) hepatocyte cells for the effect of CYLD on apoptosis? The effect of CYLD on apoptosis was assessed directly in this assay.

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Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 11644
Title: Deletion of CYLD increases resistance towards death-receptor mediated cell death in murine hepatocytes by triggering NF-κB signaling
Reviewer code: 00008233
Science editor: Ya-Juan Ma
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
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[ ] Grade D: Fair		BPG Search:	[ ] Rejection
[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Existing	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

The manuscript by Urbanik T et al. describes experiments performed to evaluate the role of the deubiquitinase CYLD in modulating apoptotic cell death in murine hepatocytes. They report that CYLD-/- mice could reduce sensitivity to apoptosis by increasing the anti-apoptotic NF-?B signalling. Authors demonstrate that CYLD -/- primary murine hepatocytes were less sensitive towards death receptor-mediated apoptosis by snowing increased levels of Bcl-2, XIAp, cIAP1/2, surviving and c-FLIP expression. Moreover, by inhibiting of NF-?B activation by BAY 11-7085 (Ikα posphorilation inhibitor) they refer an inhibition of anti-apoptotic proteins and a re-sensitization of CYLD-/- hepatocytes towards TNF- and CD95- receptor mediated apoptosis. Minor comments: 1)Authors should add in Figure 2 a clear title or a brief sentence to underline that both WT and CYLD-/- mice were treated with D-GALN/LPS (Fig. 2, panel A, B, C) or with Jo2 (Fig. 2, panel D,E,F) to facilitate the reader. 2)By performing western blotting analysis, Authors demonstrate that both in vivo (D-GALN/LPS or Jo2 injury model in CYLD-/- mice, Fig. 2 B, E) that in vitro (CYLD-/- hepatocytes, Fig. 4 D) there was a reduction of caspase 8, 9 and 3 activation. To better characterize this data, since caspases are very important in apoptosis network, it should be better if authors provide a caspase activity assay, at least of caspase 3. 3)In the Result session (page 10-11) by referring to Figure 3 B, Authors report that "p105 and p50 were expressed equally compared to WT"; by referring to Figure 3 D, upper panel, Authors state that: "…IkB-a levels were not

significantly different"; by referring to Figure 3 F, left panel, Authors state that: "...liver lysates of D-GalN/LPS treated CYLD-/- mice showed increased expression levels of the NF-kB subunits p50…". Authors should provide densitometric analysis for these western blotting or show other images more convincing to allow reader to note the really states of proteins. Some of Western blotting analysis showed in Figure 5 A (both panels) are not quite convincing: please Authors to provide densitometric analysis or better images also for these experiments. 4)Figure 5 C: Authors show Western blotting concerning the pro-caspase 3 and the caspase 3 cleaved form, but they do not cite this data on text: I suggest to add a short sentence in the test or to eliminate the image if it is not so significative.

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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Gastroenterology
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
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		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

This manuscript used gene knockout model to determine the role of Cyld in the liver under basal condition (fig 1-3) and with chemical-induced stress (fig 3-4). The results of extensive measurements are consistent with previous observations in other tissues that in the absence of Cyld, there are more growth and more responses to stress. The authors then used chemical inhibitors to determine the pathway behind the enhanced resistance to death in the absence of Clyd (fig 5). The inhibitor experiments have their limits and thus the conclusion is an oversimplified one. Perhaps the more appropriate title should be "Deletion of Cyld increases liver growth and the resistance toward stress response in murine hepatocytes"