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Wan Chai, Hong Kong, China

ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
Ms: 2333
Title: The role of activin A in the carbon tetrachloride-induced acute liver injury in mouse
Reviewer code: 00402563
Science editor: s.x.gou@wjgnet.com-1
Date sent for review: 2013-02-18 10:37
Date reviewed: 2013-03-06 22:29

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
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[Y] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS

COMMENTS TO AUTHORS:
The manuscript addresses the role of activin in an animal model of acute liver injury. As it stands, most of the manuscript is devoted to characterization of the animal disease model, which has been widely used as a model system by numerous researchers before. Therefore, most of the manuscript lacks novelty. Along the same line, the augmented presence of activin A is a common finding in all inflammatory responses in vivo, and do not constitute, by itself, a relevant or significant finding. The only original section of the manuscript is that dealing with the use of an anti-activin A antibody as a mean to inhibit the liver damage caused by CCl4. Whereas these results (Figure 5) are convincing, they are not sufficient to justify its publication as a separate scientific article. The authors should have tried to extends these preliminary findings by, at least, 1) determining the cell types responsible for activin A in liver and peripheral blood; 2) isolating liver cells from control and trated animals and evaluating the expression of activin A (and Samd and ALK4/5/7) in each specific cell type; and 3) quantify the immunohistochemistry experiments shown in Figures 1 and 5.

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
Ms: 2333
Title: The role of activin A in the carbon tetrachloride-induced acute liver injury in mouse
Reviewer code: 00012156
Science editor: s.x.gou@wjgnet.com-1
Date sent for review: 2013-02-18 10:37
Date reviewed: 2013-03-12 16:00

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	[ ] Existed	[ ] High priority for publication
[Y] 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	[ ] Existed	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS

COMMENTS TO AUTHORS:
Wang et al. examined serum Activin level, tissue activin of the liver and message of activin, ActRIIA and Smad3. As results, in injured liver tissue these mRNA expressions increased. And anti-activin A IgG was effective for the CCL4 induced liver injury.
Major comments;
There was no explanation about relationship of these 3 parameter, how signaling transduction occurs or what is happened in the necrotic or injured hepatocyte? How does anti-activin A antibody block liver injury induced by CCl4? More deeper discussion is necessary in mechanism of CCl4 liver injury and participation of activin A. Figure 3 is obscure. Therefore, we could not understand precise change of expression of activin A. About increment of activin A of blood is really by degeneration of the hepatocytes? Is there any effect in tissues except liver by CCL4? In injured liver was the apoptosis of the hepatocytes observed? Because activin A induces directly apoptosis. In activin-Smad signaling another Smad2~7 were involved or not? By administration of CCL4 lesion area was the periportal area but by administration of anti-activin A lesion moved to intermediate zone between the portal and the central vein. Why does the phenomenon occure?

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
Ms: 2333
Title: The role of activin A in the carbon tetrachloride-induced acute liver injury in mouse
Reviewer code: 00058872
Science editor: s.x.gou@wjgnet.com-1
Date sent for review: 2013-02-18 10:37
Date reviewed: 2013-03-12 18:39

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] 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:	[Y] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS

COMMENTS TO AUTHORS:
The passage of information gathered by animals to humans (Translational Medicine)concerning the acute hepatotoxicity is a key factor for every hepatologist. Authors are kindly requested to indroduce the important concept of DILI that is so frequent among obese patients (the recent pandemia)and its unpredictability quoting the two milestone papers: A prospective study of acute drug-induced liver injury in patients suffering from non-alcoholic fatty liver disease.Hepatol Res. 2007 Jun;37(6):410-5.Drug-induced liver injury: is it somehow foreseeable? World J Gastroenterol. 2009 Jun 21;15(23):2817-33. Methods: The study was based on observations addressing 12 animals, three for each group....I suppose. This is a sort of limitation of the study that should be mentioned. If it not so, Authors should pinpoint this aspect.

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Wan Chai, Hong Kong, China

ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
Ms: 2333
Title: The role of activin A in the carbon tetrachloride-induced acute liver injury in mouse
Reviewer code: 00503536
Science editor: s.x.gou@wjgnet.com-1
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Date reviewed: 2013-03-17 15:16

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] 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:	[Y] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS

COMMENTS TO AUTHORS:
The manuscript written by Wang et al. reports the role of activin A in the pathogenesis of CCl4-induced liver injury. They found that the levels of activin A in the blood and the liver and the expression of mRNAs for activin A, activin type IIA receptor and Smad3 in the liver were increased after CCl4 injection. They also performed blocking experiment with anti-activin Ab, and found that CCl4-induced liver injury can be inhibited by the administration of the Ab. The experiments are well-organized, and these data are could give important information on the pathogenesis treatment of liver injury. However, there are some concerns that need to be addressed.
Major points,
1.The liver histology in Fig 3 shows activin A expression in the liver after CCl4 injection. However, the areas rich in hepatocytes injury and the areas expressing activin A are inconsistent. The authors should make a comment on that point.
2.The nuclei of hepatocytes positive for activin A look larger than that of activin-negative hepatocytes. The authors should mention on that point in regard to the effect of activin overexpression in hepatocytes.
3.Did the authors examine the expression of apoptosis-related molecules in hepatocytes or perform TUNEL assay in liver tissues?
4.The inhibition of CCl4-induced liver injury by the administration was only partial, although it was statistically significant. The authors should mention how important activin A is in the pathogenesis of the liver injury.

Minor point

1.In figure 3, original magnification of each photograph should be shown. In addition, it should be mentioned that D and F are the same liver tissues of C and E, respectively, but only magnification is different.

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
Ms: 2333
Title: The role of activin A in the carbon tetrachloride-induced acute liver injury in mouse
Reviewer code: 00202486
Science editor: s.x.gou@wjgnet.com-1
Date sent for review: 2013-02-18 10:37
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] 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	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS

COMMENTS TO AUTHORS:
The authors investigated the expression and role of activin A in acute chemical liver injury in mouse. They concluded that activin A was involved in CCl4-induced liver injury in an autocrine/paracrine manner, and furthermore, blockade of activin A biological action could be potential therapeutic approach for acute liver injury. Overall, the quality of the data in this manuscript was good, and it has proper controls. However , some additional experiments may be needed to further address the role of activin A in CCl4-induced liver injury. In addition, it would be greatly improved the quality of this manuscript if the authors would be able to provide some mechanistic insight regarding the mechanisms of biological action of activin A.
Major Concerns:
1. It seems that CCl4-induced necrosis mainly occurred in Day 1, while inflammation occurred in Day 3 (Figure 1). While the anti-activin antibody seemed to be protective against CCl4 hepatotoxicity based on the ALT levels (Figure 5) and inflammation (Figure 5 H&E staining). It would be very helpful if the authors could provide the data on Day 1 to see whether anti-activin antibody would also attenuate CCl4-induced necrosis. There were some differences in the ALT levels between Figure 1 and Figure 5. It is not clear whether this was due to the administration of IgG. A group only given CCl4 should also be included.
2. Figure 4: Authors claimed that activin-ActRIIA-Smad signal transductions might be activated. However, iIncreased mRNA levels don't necessarily correlate with protein levels or activation of signal transduction pathway. It would be helpful to determine the protein levels by western blot.

Minor concerns:

1. The English writing of this manuscript needs to be improved. The authors are encouraged to seek help from native English speaking people or other professionals.

a. Page 3 Line 60-61: "…. it is an important factor to lead to liver fibrosis." It would be better to revise to "it is an important factor in liver fibrosis development."

b. Page 4 Line 69: "and" needs to be inserted before "olive oil".

c. Page 5 Line 98: aprotitin is spelled wrong. Change to "aprotinin".

d. Page 8 Line 165: "in injury liver of..." Injury needs to be changed to " injuried "

e. Page 8 Line 166: change "no necrotic area" to "non-necrotic area".

f. Page 9-10 Line 198-199: "Activin A combines directly with..." Combines needs to be changed to" interacts".

g. Page 11 Line 231: "potential therapeutic clue for acute liver injury diseases." This is awkward phrase. It could be reworded to something like "potential therapeutic approach for acute liver injury."

2. Figure 3: RT-PCR data. The authors used % of control. Fold change of control is the standard way of analyzing RT-PCR data.

3. Figure 5 Legend: What is the p value?