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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 6631
Title: Recent insights into the mechanisms of alcohol fatty liver disease
Reviewer code: 02822528
Science editor: Ya-Juan Ma
Date sent for review: 2013-11-14 22:22
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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	[ ] 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 TO AUTHORS

In this manuscript, the author summarized the classical concepts about the pathogenesis of AFLD and the role of TNF-α in ALD, in the induction of fatty liver, and then stated that activated Kupffer cell-derived TNF-α over-production was responsible for the dysregulated SREBP-1, PAI-1, Egr-1, and PPAR-α activity, which lead to the dysfunction of lipid metabolism in alcoholic fatty liver. The author also summarized that bone marrow-derived cell and sympathetic hyperactivity-activated hepatic stellate cell were responsible for TNF-α overproduction in alcoholic fatty liver. In addition, the author reported that carvedilol might attenuate the progression of alcoholic fatty liver by suppressing sympathetic activity. This article is well written and interesting. However, there are some concerns remain. 1) The author stated that TNF-α overproduction induced AFLD. It is well known that TNF-α overproduction is closely coupled with alcoholic liver injury. However, the role of TNF-α in the induction of AFLD remain uncertain. Whether it is a primary player or whether its appearance is secondary to hepatic injury? It seems more likely that TNF-α promotes the progression of alcoholic liver disease rather than initiates fat accumulation in the liver. Please commentate. 2) Although endotoxin-induced systemic inflammatory state can reduce PPAR-α expression, the author did not cite any reference to directly support his statement that TNF-α overproduction is responsible for the decrease of PPARα activity in alcoholic fatty liver. It is better for the author not to state that activated Kupffer cell-derived TNF-α over-production is responsible for the dysregulated PPARα activity. 3) On page 5, line 1-4, the author took PAI-1 as transcriptional factor. However, PAI-1 is not a transcriptional factor. 4) On page 9, line 20, the sentence "TNF-α has been shown to increase hepatic lipid synthesis by an increase in lipolysis" is confusing.

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ESPS Peer-review Report
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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 TO AUTHORS

In this manuscript Dr. Liu et al. have clearly described the recent insights into the mechanisms of alcoholic fatty liver disease. I can recommend one major issue that authors should focus on why some heavy drinkers do not progress to alcoholic steatohepatitis, although some mild alcoholics do? This mechanism may explain the complexity and multifactorial reasons underlying in the pathogenesis of AFL. Minor issues; 1. In title, instead of 'alcohol' authors should use 'alcoholic'. 2. Instead of the 1st reference that is from 2004, authors should use the new reference that reflects the new prevalence of the alcohol intake of all deaths worldwide. 3. In the last paragraph of introduction, authors should change one of the β1 as β2. Best,

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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	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)		BPG Search:	[Y] Minor revision
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

The study is aimed to review the classical concepts about the pathogenesis of alcoholic fatty liver disease (AFLD) and the recent insights into the mechanisms of this pathologic condition. It focused on the role of tumor necrosis factor alfa (TNF-α), sympathetic hyperactivity-activated hepatic stellate cells, and bone marrow-derived cells in the induction of fatty liver. This is a big review easy to read with 142 classic and current references. The text is divided in topics allowing an update on the subject and clarifying the limitations of the evidences presented. The author suggested that the understanding of these mechanisms could generate therapeutic interventions to reduce the progression of AFLD, however these possibilities were not well explored. He talks about the treatment with IL-6 and carvedilol, although there is no information regarding therapeutics with Pentoxifylline, anti-oxidant agents, anti-TNF-α for example. Also adding brief comments on these therapies under clinical perspective might make the article more interesting and complete for clinicians. Below are some articles which exploit the above mentioned therapies. Ashwin D Dhanda, Richard WL Lee, Peter L Collins, C Anne McCune. Molecular targets in the treatment of alcoholic hepatitis. World J Gastroenterol 2012; 18(39): 5504-5513. Stewart S, Prince M, Bassendine M, et al. A randomized trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis. J Hepatol 2007;47:277-283. Phillips M, Curtis H, Portmann B, Donaldson N, Bomford A, O'Grady J. Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis – a randomised clinical trial. J Hepatol 2006;44:784-790. Spahr L, Rubbia-Brandt L, Frossard JL, et al. Combination of steroids with infliximab or placebo in severe alcoholic hepatitis: a randomized controlled pilot study. J Hepatol 2002;37:448-455. Tilg H, Jalan R, Kaser A, et al. Anti-tumour necrosis factor-alpha

monoclonal antibody therapy in severe alcoholic hepatitis. J Hepatol 2003;38:419-425. Naveau S, Chollet-Martin S, Dharancy S, et al. A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. Hepatology 2004;39:1390-1397. Sharma P, Kumar A, Sharma BC, Sarin SK. Infliximab monotherapy for severe alcoholic hepatitis and predictors of survival: an open-label trial. J Hepatol 009;50:584-591. Menon KV, Stadheim L, Kamath PS, et al. A pilot study of the safety and tolerability of etanercept in patients with alcoholic hepatitis. Am J Gastroenterol 2004;99:255-260. Boetticher NC, Peine CJ, Kwo P, et al. A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcohol hepatitis. Gastroenterology 2008;135:1953-1960. Whitfield K, Rambaldi A, Wetterslev J, Gluud C. Pentoxifylline for alcoholic hepatitis. Cochrane Database Syst Rev 2009;(4):CD007339. Parker R, Armstrong MJ, Corbett C, Rowe IA, Houlihan DD. Systematic review: pentoxifylline for the treatment of severe alcoholic hepatitis. Aliment Pharmacol Ther 2013 Mar 13. Lebrec D, Thabut D, Oberti F, et al. Pentoxifylline does not decrease short-term mortality but does reduce complications in patients with advanced cirrhosis. Gastroenterology 2010;138:1755-1762.

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
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[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

My comments: In this manuscript, Dr. Liu reviewed recent insights into the mechanisms of alcohol fatty liver disease. This paper is interesting and provides a new idea to the prevention and treatment of alcohol fatty liver disease (AFLD). The author searched out one of the important factors through the analysis of recent study about AFLD, and believed that TNF-α overproduction mainly contributed to the occurrence and development of AFLD. The author suggested that combination therapy of carvedilol （nonselective beta blocker/alpha-1 blocker ）and a TNF-α inhibitor may be effective in the treatment of patients with AFLD. However, there are some defects in this manuscript. Firstly, the title is too large, this reviewer is mainly focused on AFLD and TNF-α, I suggest the author grasp this main idea and fully discuss the relationship between AFLD and TNF-α, whether it is a cause or whether its appearance of AFLD? Secondly, I suggest the author discuss the difference of AFLD and NAFLD. Moreover, the author did not point out the different roles of TNF-α in AFLD and other diseases. It is well known that TNF-α participates in the normal inflammatory response and immune response as well as pathological condition. TNF-α overproduction can occur in many diseases，for instance, Rheumatoid arthritis（RA）、ulcerative colitis（UC）and so on. TNF-α inhibitor has been used for the treatment of some diseases, such as RA and UC. What is the difference in the treatment of AFLD and other diseases? There are a series of problems to be solved in practical applications of TNF-α inhibitor. In my opinion ,the author should analyze these differences briefly. It is better to make evaluation for the treatment of AFLD. In summary, despite these defects, this paper is well-organized and easy to read. It brings us new ideas to solve the clinical problems of AFLD.