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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 6509
Title: Translational approaches to NAFLD and NASH: where do we stand
Reviewer code: 00503544
Science editor: Ma, Ya-Juan
Date sent for review: 2013-10-22 18:37
Date reviewed: 2013-11-02 12:30

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

COMMENTS TO AUTHORS

In the present paper, the authors review the pathogenesis and in-vivo and in-vitro experimental models of nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH). As the authors point out, NAFLD/NASH is rapidly increasing all over the world and it may progress to liver cirrhosis and hepatocellular carcinoma. Thus, the elucidation of the pathogenesis of the disease by using experimental models is important. Therefore, this review article deals with an important topic. However, the authors should consider the following points. 1. Several widely used animal models are not mentioned in this paper. The authors should mention KK-Ay mice, high-cholesterol and cholate diet model, and high-fructose diet model. 2. Genetic models, dietary models, and combination models are mixed up in Table 1. The authors should arrange the table more systematically. 3. The quality of English is a little poor. The authors should seek assistance of a native English speaker.

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
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Title: Translational approaches to NAFLD and NASH: where do we stand
Reviewer code: 00227342
Science editor: Ma, Ya-Juan
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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

The article by Rosso and co-workers, entitled "Translational approaches to NAFLD and NASH: where do we stand" is very interesting review article. The article is well written. Furthermore, it correctly cites the most important articles in the field. I would suggest some minor points that can be ameliorated: Major points: 1. In the paragraph entitled "Pathogenesis", the authors might refer to the role of inflammation citing some publications also summarized in the recent review by Braunersreuther V, et al. (World J Gastroenterol. 2012;18:727-35) and Carbone F et al. (Thromb Haemost. 2013;110:940-58). 2. The pro-inflammatory role of insulin can be discussed in the paragraph entitled "Pathogenesis" reporting studies investigating the activity of this hormone on inflammatory and vascular cells involved in atherogenesis (Montecucco F, et al. Am J Physiol Endocrinol Metab. 201;300:E681-90; Bunn RC, et al. Cardiovasc Diabetol. 2010;9:73; Gage MC, et al. Atherosclerosis. 2013;230:131-9). Paradoxical effects of insulin can be also described (Tsuchiya K, et al. Cell Metab. 2012;15:372-81).

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 6509
Title: Translational approaches to NAFLD and NASH: where do we stand
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Science editor: Ma, Ya-Juan
Date sent for review: 2013-10-22 18:37
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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	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

Major points; 1. Authors should explain and discuss the studies about the mitochondrial dysfunction. Because, it is important for hepatocellular injury in patients with NAFLD. 2. Authors should also focus on the issue that why some slim shaped patients with NAFLD progress to the NASH and why some obese patients do not? 3. What do the authors think about the role of hepatic stellate cell or kuppfer cell (collagen metabolism) for the transition from simple steatosis to steatohepatitis? Minor points; 1. To improve the quality of the written English, authors should take the assistance of a native English speaker. Regards.

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
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Title: Translational approaches to NAFLD and NASH: where do we stand
Reviewer code: 02541483
Science editor: Ma, Ya-Juan
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[Y] 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
[ ] 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

This is an interesting review on translational approaches from fatty liver to non alcoholic steatohepatitis. The article contributes to better understanding of the molecular mechanism associated to the accumulation of fatty acids in the liver cell, what is known and what is still to be discovered on the events related to the accumulation of fat within the liver and the resulting damage. However, I have some remarks: 1. Insulin Resistance (IR) should be written as insulin resistance (IR). 2. Who is calculated that in the next 40 years the daily caloric requirements will decrease of 350 calories (reference?) 3. In Pathogenesis section insulin resistance should be written as IR. All abbreviations should be explained only the first time they appeared in text! 4. In Pathogenesis section Type 2 Diabetes Mellitus should be written as type 2 diabetes mellitus. 5. Not only MS, but also fatty liver is independently associated with chronic kidney disease and progression of other microvascular complications in T2DM (Targher G, Chonchol M, Zoppini G, Abaterusso C, Bonora E. Risk of chronic kidney disease in patients with non-alcoholic fatty liver disease: Is there a link? J Hepatol 2011; 54: 1020-9; Targher G, Bertolini L, Rodella S, Zoppini G, Lippi G, Day C i sur. Non-alcoholic fatty liver disease in independently associated with an increased prevalence of chronic kidney disease and proliferative/laser treated retinopathy in type 2 diabetic patients. Diabetologia 2008; 51: 444-509). 6. Treatment with GLP-1 agonist exenatide resulted in a reduction of hepatic fat quantity and hepatic biomarkers in T2DM: K. Blaslov, K. Zibar, T. Bulum, L. Duvnjak. Effect of exenatide therapy on hepatic fat quantity and hepatic biomarkers in type 2 diabetic patients. Clinics and Research in Hepatology and Gastroenterology 2013; DOI: 10.1016/j.clinre.2013.10.013. This reference should be added. 7. Authors state that monocytes are activated by conditions of hyperinsulinemia and

abnormal levels of FFA encountered in individuals with IR, contributing to the development of complications such as T2DM. Monocytes are also associated with IR in autoimmune type 1 diabetes, and in those subjects IR is independently associated with markers of NAFLD (T. Bulum, B. Kolari?, L. Duvnjak, M. Duvnjak. Nonalcoholic fatty liver disease markers are associated with insulin resistance in type 1 diabetes. Digestive Diseases and Sciences 2011; 56: 3655-3663; T. Bulum, B. Kolari?, L. Duvnjak. Decreased serum monocytes and elevated neutrophils as additional markers of insulin resistance in type 1 diabetes. International Journal of Diabetes in Developing Countries 2013; DOI: 10.1007/s13410-013-0176-5). It think that it would be useful to stress that IR is not only associated with fatty liver in MS related disorders like T2DM, but also in those that are not closely associated with MS like type 1 diabetes, according to mentioned studies. 8. In In-vivo and in-vitro Experimental models section metabolic syndrome should be written as MS. 9. Figure 1: estimation of the past, present and future of the major etiologies incidence of chronic liver diseases is based on what source? Is this original table from authors as well as Figure 2 and Figure 3?

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
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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

GENERAL COMMENT The topic is timely and the manuscript is well written. I have just some comments aimed at improving this excellent submission. SPECIFIC COMMENTS The Authors might be willing to address the following topics: a) In rodents, given sufficient time, NASH will develop from pure steatosis provided that the offending agent (e.g. High-fat diet) is not removed. This occurs at variance with human disease, where pure steatosis and NASH are probably born as different and "unrelated" disorders (Yilmaz Y. Review article: is non-alcoholic fatty liver disease a spectrum, or are steatosis and non-alcoholic steatohepatitis distinct conditions? Aliment Pharmacol Ther. 2012;36:815-23. Caldwell S et al. Perspectives on cellular dysfunction in nonalcoholic steatohepatitis: a case of 'multiorganelle failure'? Proceedings of a virtual workshop on nonalcoholic steatohepatitis. Expert Rev Gastroenterol Hepatol. 2011;5(2):135-9.). b) Highlight those animal models which more closely resemble human disease (e.g. Kechagias S, et al. Fast-food-based hyper-alimentation can induce rapid and profound elevation of serum alanine aminotransferase in healthy subjects. Gut. 2008;57:649-54. c) Are there any relevant differences in NAFLD such as observed in different animal species, e.g. birds, rodents and mammals ? (Insulin resistance in non-alcoholic fatty liver disease: a clinical perspective Carulli N, et al. Leuschner et al Eds- FALK SYMPOSIUM 121, 2001 pages 104-113; Caldwell SH, et al. Has natural selection in human populations produced two types of metabolic syndrome (with and without fatty liver)? J Gastroenterol Hepatol. 2007 Jun;22 Suppl 1:S11-9.; Cohen JC, et al. Human fatty liver disease: old questions and new insights. Science. 2011;332:1519-23.) d) Insulin resistance appears to be a "necessary though not sufficient" trigger in the development of NAFLD (Ratziu V, et al. Insulin

resistance in nonalcoholic steatohepatitis: necessary but not sufficient - death of a dogma from analysis of therapeutic studies? Expert Rev Gastroenterol Hepatol. 2011;5:279-89.) e) There are two more pathogenic theories that need to be shortly alluded to: Wanless IR, et al. The pathogenesis of nonalcoholic steatohepatitis and other fatty liver diseases: a four-step model including the role of lipid release and hepatic venular obstruction in the progression to cirrhosis. Semin Liver Dis. 2004;24:99-106.; Caldwell SH, et al. Clinical physiology of NAFLD: a critical overview of pathogenesis and treatment Expert Review of Endocrinolgy and Metabolism 2010). f) The different effects of palmitic and oleic acid in hepatocitic cell cultures need to be mentioned (Ricchi M, et al. Differential effect of oleic and palmitic acid on lipid accumulation and apoptosis in cultured hepatocytes. J Gastroenterol Hepatol. 2009;24:830-40.) g) Are there are any particularly relevant animal models to be discussed in some detail ? (E.G. ob/ob and LIRKO) h) Are the Authors aware of any animal models using mipomersen ? This drug may mimic familial hypobetaliproteinemia. i) The sub-title resembles several previously published papers and needs to be changed. j) All English mother tongue Authors invariably use the word “evidence” as a singular (i.e. collective) noun and never as plural such as tpycally used in neo-latin languages.

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
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Reviewer code: 02861137
Science editor: Ma, Ya-Juan
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[Y] 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	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

Thank you for addressing me this article that aimed to review the in-vivo and in-vitro experimental models of NAFLD and NASH for a better knowledge of its pathogenesis. A better knowledge of this topic is very important to understand the pathogenesis of NAFLD and consequently prevent the evolution from simple steatosis to NASH. The topic was well covered. Major points of the biological pathway and the role of proinflammatory cytokines and atherogenic molecules were well described on the "Pathogenesis" section. The most important in-vivo and in-vitro experimental models were included and essential references were cited. Minor points: (i) the abusive use of abbreviation leads to a hard lecture; (ii) few words were not spelled before abbreviation (i.e. FFA on page 6; definition of FFA on page 9); (iii) authors should at least include an abbreviation section; (iv) English language should be improved. Best Regards

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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
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] 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

This manuscript deals with an important health issue and therefore is of great interest for medical doctors and scientists. It covers both the pathogenesis and the in vivo and in vitro models of NAFLD and NASH with the aim of developing a translational approach from the lab bench to the clinical practice. Overall, the manuscript is very interesting although it should be better organized in order to facilitate the reader in the comprehension of the different aspects treated. To this aim, it is advisable to organize the text in distinct paragraphs and to report the results in distinct tables for the in vitro and in vivo studies. In any case, it is important to report the reference for each model listed in Table 1. Furthermore, when speaking of high fat diet, other studies could be quoted, such as Ferramosca et al. 2013, Eur. J. Nutr. in press and 2012 PLoS One 7, e38797.