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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 44639

Title: Dynamic changes of key metabolites during liver fibrosis in rats by ultra-performance liquid chromatography-mass spectrometry

Reviewer's code: 02537403

Reviewer's country: Romania

Science editor: Xue-Jiao Wang

Date sent for review: 2018-11-21

Date reviewed: 2018-11-29

Review time: 17 Hours, 8 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

The study performs a comprehensive analysis of liver fibrosis, as predictor of significant morbidity and mortality in patients with chronic liver disease, by assessing dynamic changes of different metabolic pathways and serum levels of biomarkers during fibrosis

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progression using rat models. Metabolites changes were dynamically investigated during the process of liver fibrosis development, based on pathological findings. The novelty of the research consists in identification of two serum biomarkers, muricholic acid (MCA) and cervonoyl ethanolamide (CEA), which proved to be relevant for assessing fibrosis in an animal model and showed superior accuracy in discriminating early vs. advanced fibrosis. Using ROC analyses, these novel biomarkers proved to be effective in framing both early and intermediate cirrhosis stages vs. currently used biomarkers. Therefore, this is an original manuscript that opens new doors in identifying novel and more accurate biomarkers for staging liver fibrosis that may replace in the future liver biopsy, considered as a gold standard but an invasive method for assessing fibrosis. I would recommend that the paper should focus more on describing currently available non-invasive tests for staging fibrosis and to stress on the advantages of these new biomarkers in comparison to the available non-invasive tests (not only the conventional functional liver tests), e.g superiority in identifying early fibrosis or discrimination between early/intermediate stages of fibrosis.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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[ ] Duplicate publication

[ ] Plagiarism

[Y] No

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[ ] Plagiarism

[Y] No

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 44639

Title: Dynamic changes of key metabolites during liver fibrosis in rats by ultra-performance liquid chromatography-mass spectrometry

Reviewer's code: 03647148

Reviewer's country: Taiwan

Science editor: Xue-Jiao Wang

Date sent for review: 2018-11-21

Date reviewed: 2018-12-05

Review time: 9 Hours, 14 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
[Y] Grade D: Fair	[ ] Grade D: Rejection	[Y] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript entitled "Dynamic changes of key metabolites during liver fibrosis in rats" focused on dynamic changes in metabolic profiles and biomarker concentrations in rat serum during liver fibrosis progression by using ultra-performance liquid

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chromatography coupled to quadrupole time-of-flight mass spectrometry. Although the study has been done very well, the proteomic studies on liver fibrosis or cirrhosis are not new. Besides, there are many problems in the manuscript needed to be solved before publication. Major revisions: 1. The only new in this study is to find out two serum markers in only one animal model but no ex vivo or in vitro studies in the manuscript to confirm the functional or clinical implications of the two proteins. Besides, only one animal study was so week to support the novel role of these proteins on liver fibrosis and cirrhosis. The authors should add another model to reproduce their experiment to get the same results and to confirm their important role. The standard evaluation of the animal model should include the fibrosis score which the authors did not mention in the manuscript. The authors did not define which group is fibrosis or cirrhosis. The authors may consult pathologist for the reading of their tissue pathology and hepatologist for the interpretation of clinical implications of the two proteins, who could be included in the coauthor. 2. The authors did not investigate the functional effects of the two proteins. Therefore, the authors can only cite references to explain the clinical relationship between the two proteins and the manifestation of liver fibrosis or cirrhosis. 3. The discussion is mostly descriptive. There is much hypothesis the authors have to do functional study or check serum levels, such as TNF- , INF- and IL-17 or TBA, to confirm the importance of the two proteins. 4. Actually, there have been many studies and reviews to report the proteomics of liver fibrosis and cirrhosis and many serum markers were reported. What is the difference between the previous reports and this study? Is there any relationship between them? Anyway, these studies or reviews should be added in the introduction or discussion section. 5. A recently published paper in International Journal of Biological Macromolecules Volume 111, May 2018, Pages 379-392 (Proteomic-genomic adjustments and their confluence for elucidation of pathways and networks during liver fibrosis), is a good reference the authors may be

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interesting. Minor revisions: 1. There are many subtypes of MCA reported and the most important one is beta-MCA. Can the authors tell reader which subtype of MCA is most important in their study? 2. Before resubmitting, the authors should send the manuscript for English-editing.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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[ ] Plagiarism

[Y] No

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 44639

Title: Dynamic changes of key metabolites during liver fibrosis in rats by ultra-performance liquid chromatography-mass spectrometry

Reviewer's code: 00004696

Reviewer's country: United States

Science editor: Xue-Jiao Wang

Date sent for review: 2018-11-21

Date reviewed: 2018-12-09

Review time: 12 Hours, 18 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Enjoyed reviewing this manuscript but have a few comments. Authors appeared to have complied with 14 points for peer-review checklist. Introduction: 1. Delete invasive ('invasive' liver biopsy) 2. Limited availability for non-invasive monitorting of liver

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fibrosis.This is not accurate as clinical trials are now using non-invasive tests such as fibroscan and MRI to monitor hepatic steatosis and fibrosis in lieu of liver biopsies. I think this sentence needs to be rewritten. Results: Authors state cholestatic liver chemistries increased less rapidly than hepatocellular enzymes.However, no explanation for this observation was reported in the discussion and would be important for readers. 3.2 Bubble -like morphological changes in liver: not familiar with this term. Did authors mean balloon degeneration of hepatocytes? Investigators used MTC staining performed for collagen staining at predetermined intervals which is acceptable. However, Western blotting is used to detect alpha actin, a sign of stellate cell activation and an events which occurs much earlier before deposition of fibrosis.Could investigators explain why this was not performed? 3.5 Profiles most dramatic at early stage of disease yet in discussion authors state most severe metabolic changes were noted at the final stages. Confusing and needs to be clarified. Discussion: Sentence on ROS and hepatocyte necrosis, cell permeability , steatosis, cirrhosis can be deleted. Final paragraph needs writing. For example CEA is an agonist against CB2 (ie do you mean antagonist?) . Would consider rewriting sentence 'This study identified two novel biomarkers, CEA and MCA involved in x and y, that are able to etc. I would accept this manuscript for publication after the above changes are made. Thank you for offering me the opportunity to review this manuscript.

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