



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 39364

Title: The Role of MicroRNAs in Alcohol-Induced Liver Disorders and non-Alcoholic Fatty Liver Disease

Reviewer’s code: 01555255

Reviewer’s country: Italy

Science editor: Xue-Jiao Wang

Date sent for review: 2018-04-16

Date reviewed: 2018-04-18

Review time: 2 Days

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 Grade E: Do not publish	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

SPECIFIC COMMENTS TO AUTHORS

1. Be consistent with NF-κB (sometimes it’s NFκB). 2. PNPLA3 on page 7 needs to be italicized (PNPLA3), as all the names of microRNAs. 3. “SIRT1 inhibits the co-activator 1 alpha of the PPAR-gamma (PPAR-alpha)”: the sentence is not clear, PPAR-gamma and



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PPAR-alpha are two distinct isoforms of PPAR, it would be better to remove "(PPAR-alpha)". 4. General comment (1): the authors should probably provide some further comments on the fact that the role of microRNAs is a critical bridge between genome and environment. They mentioned some SNPs reported in microRNAs that may be associated with increased risk of liver diseases, but more complex regulatory networks are involved at the epigenetic level to modulate the expression of microRNAs and their downstream targets. Furthermore, dynamic fluctuations of miRNA levels are influenced by environmental factors such as alcohol (discussed), but also diet, drugs, and cigarette smoking. It has been proof that a high-caloric diet and/or chronic smoking predispose to increased oxidative metabolism, leading to a pro-inflammatory profile of released miRNAs and cytokines. 5. General comment (2): perhaps the authors could provide some more information on the interaction of miRNAs and SIRT1 with the Keap1/Nrf2 system, regulating the anti-oxidant regulatory elements (AREs) and coordinating the cellular response to ROS and oxidative stress. Here is some related literature: a) Boccuto L, Abenavoli L. Genetic and Epigenetic Profile of Patients With Alcoholic Liver Disease. *Ann Hepatol.* 2017 Jul-Aug;16(4):490-500. b) Yang D, Tan X, Lv Z, Liu B, Baiyun R, Lu J, Zhang Z. Regulation of Sirt1/Nrf2/TNF- α signaling pathway by luteolin is critical to attenuate acute mercuric chloride exposure induced hepatotoxicity. *Sci Rep.* 2016 Nov 17;6:37157. c) Wan C, Han R, Liu L, Zhang F, Li F, Xiang M, Ding W. Role of miR-155 in fluorooctane sulfonate-induced oxidative hepatic damage via the Nrf2-dependent pathway. *Toxicol Appl Pharmacol.* 2016 Mar 15;295:85-93. d) Kurinna S, Werner S. NRF2 and microRNAs: new but awaited relations. *Biochem Soc Trans.* 2015 Aug;43(4):595-601. e) Shi L, Wu L, Chen Z, Yang J, Chen X, Yu F, Zheng F, Lin X. MiR-141 Activates Nrf2-Dependent Antioxidant Pathway via Down-Regulating the Expression of Keap1 Conferring the Resistance of Hepatocellular Carcinoma Cells to 5-Fluorouracil. *Cell Physiol Biochem.* 2015;35(6):2333-48. f) Yang JJ,



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Tao H, Hu W, Liu LP, Shi KH, Deng ZY, Li J. MicroRNA-200a controls Nrf2 activation by target Keap1 in hepatic stellate cell proliferation and fibrosis. *Cell Signal*. 2014 Nov;26(11):2381-9.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

- The same title
- Duplicate publication
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- No

BPG Search:

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 39364

Title: The Role of MicroRNAs in Alcohol-Induced Liver Disorders and non-Alcoholic Fatty Liver Disease

Reviewer’s code: 01808881

Reviewer’s country: United States

Science editor: Xue-Jiao Wang

Date sent for review: 2018-04-24

Date reviewed: 2018-04-24

Review time: 20 Hours

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

SPECIFIC COMMENTS TO AUTHORS

This is an informative review of miRNAs in ALD and NAFLD to illustrate their utility as biomarkers or therapeutic targets. The authors rightfully conclude that several technical limitations including the promiscuous nature of the miRNAs and the lack of specificity



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preclude their clinical use. Can the authors explain the while secretion of miRNAs in exosomes (e.g. miR-122) can cause an increase in inflammatory response by targeting monocyte/macrophage cells, treatment with antiMIR122 recapitulates and augments the hepatocellular damage and steatosis induced by chronic alcohol and in combination with alcohol worsened ALD pathology as recently reported (Gastroenterology 2018, 154:238). Further, discuss why Miravisen, a miR122 inhibitor shows promising results in chronic hepatitis treatment. This information should be put together into some logical explanation. This is well explained for NAFLD but not for ALD which should be done.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 39364

Title: The Role of MicroRNAs in Alcohol-Induced Liver Disorders and non-Alcoholic Fatty Liver Disease

Reviewer's code: 02528832

Reviewer's country: Spain

Science editor: Xue-Jiao Wang

Date sent for review: 2018-04-24

Date reviewed: 2018-04-28

Review time: 4 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
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<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

An interesting study, well structured and organized. However, authors should clarify the sentence on page 7 of the main body of the manuscript, under the heading miR-34a, lines 5-6, relative to the effects. of SIRT1 on PGC 1 alpha (or PPAR alpha?)



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