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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 52065

Title: FGF signaling in NAFLD and NASH – paving the way to HCC

Reviewer's code: 01555255
Position: Editorial Board
Academic degree: MD, MSc, PhD
Professional title: Associate Professor
Reviewer's country: Italy
Author's country: Germany

Reviewer chosen by: Jin-Zhou Tang
Reviewer accepted review: 2019-11-18 09:43
Reviewer performed review: 2019-11-18 10:21
Review time: 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] 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[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced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

Lactobacillus rhamnosus GG administration increases hepatic FGF21 expression and

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serum adiponectin concentration, resulting in a reduced carbohydrate responsive-element binding protein activation through dihydrosphingosine-1-phosphate-mediated protein phosphatase 2A deactivation, and subsequently reversed fructose-induced NAFLD. Literature data suggest that FGF21 is required for the beneficial effects of LGG in reversal of fructose-induced NAFLD. Please include it in the text. Also i suggest to include a table with studies on different FGF and its action in the development of NAFLD/NASH.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 52065

Title: FGF signaling in NAFLD and NASH – paving the way to HCC

Reviewer's code: 04091933
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Associate Professor, Senior Researcher
Reviewer's country: Russia
Author's country: Germany

Reviewer chosen by: Jin-Zhou Tang
Reviewer accepted review: 2019-11-17 21:45
Reviewer performed review: 2019-11-30 19:49
Review time: 12 Days and 22 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] 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

The manuscript is very relevant as the global burden of NAFLD is increasing. A

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manuscript can be published after a minor revision. The role of FGFs as potential biomarkers of NAFLD/NASH should be reflected, at least minimally. Refs. to articles of 2019 (there are only two Refs.) are recommended to be added (for example, Praktiknjo M. et al., 2019; Barb D. et al., 2019). In addition, I would advise that scientific information on factors other than FGF19 (FGF15/19) or FGF21, in particular, FGF1 and FGF23 be given. Although the author writes that 'FGF23 is linked to calcium and phosphate homeostasis in bone and kidney via α-Klotho co-signaling and not considered to play an important role in liver pathophysiology', some studies showed the association of serum FGF23 and NAFLD (He X. et al., 2018). An experimental study in mouse model has demonstrated that FGF1 may be therapeutically effective in NAFLD (Liu W. et al., 2016). Other clinical studies on FGFs should be added (for example, a recent study that showed that NGM282 improved the histology and fibrosis in patients with NASH [Harrison S.A. et al., 2019]). Ideally, experimental studies in animal models should also be given. Given the role of microbiota in the pathogenesis of NAFLD/NASH, available scientific data on the association between microbiome, some probiotic bacteria (LGG), microbially transformed bile acids and some FGFs/FGFRs (FGFR4) would be desirable (Jiao N. et al., 2018; Liu Y. et al., 2019; Zhao C. et al., 2019).

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 52065

Title: FGF signaling in NAFLD and NASH – paving the way to HCC

Reviewer's code: 00049727
Position: Editorial Board
Academic degree: MD
Professional title: Associate Professor
Reviewer's country: Japan
Author's country: Germany

Reviewer chosen by: Jin-Zhou Tang

Reviewer accepted review: 2019-11-17 13:43

Reviewer performed review: 2019-12-01 09:59

Review time: 13 Days and 20 Hours

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

Prof. Ocker provides a detailed description on how the FGF15 subfamily plays a role in

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NAFLD/NASH and ensuing HCC. However, there are some points to be corrected and revised. 1. HCC usually occurs in the context of cirrhosis. Some studies have shown that hepatocytes in healthy liver rarely express FGF1 or FGF2, but FGF1 and FGF2 are induced in chronic liver disease and HCC. FGF2 stimulates HCC proliferation through autocrine mechanism and enhances angiogenesis and HCC invasion. Ectopic expression of FGFR1 is also frequently observed in HCC cells. Moreover, FGF1 and FGF2 are involved in hepatic stellate cell activation, which may be a key link in the induction of HCC by NAFLD/NASH. The author should add these statements. 2. In addition, members of the FGF8 subfamily (FGF8, FGF17 and FGF18) also showed carcinogenic effects on HCC. These FGFs and receptor expressions are up-regulated in HCC. Four FGF8 isoforms and FGF17 and FGF18 have great affinity with FGFR2, FGFR3 and FGFR4. The FGF8 subfamily (FGF8, FGF17 and FGF18) is involved in autocrine and paracrine signaling of HCC and can enhance the survival of tumor cells under stress conditions, malignant behaviors and new angiogenesis. I think it is also one of the important links for the development of NAFLD/NASH to HCC. The author should add these points. 3. FGF19-FGFR4 axis is an important target for treating HCC, but FGF1, FGF2 and FGF8 subfamilies and their receptors may also be important members of the anti-HCC. The author should add these statements. 4. I recommend to summarize the role of FGF/FGFRs on NAFLD/NASH and HCC as Tables. 5. There are some typographical errors, such as “polyunsatturated”. Please check carefully before re-submission.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 52065

Title: FGF signaling in NAFLD and NASH – paving the way to HCC

Reviewer's code: 00058441
Position: Editorial Board
Academic degree: PhD
Professional title: Associate Research Scientist
Reviewer's country: Taiwan
Author's country: Germany

Reviewer chosen by: Jin-Zhou Tang

Reviewer accepted review: 2019-11-18 13:51

Reviewer performed review: 2019-12-02 10:15

Review time: 13 Days and 20 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[Y] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[Y] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] 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	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

I have only two comments: 1. page3,"Binding of FGFs leads to receptor dimerization and

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activation of the downstream signaling cascade that mediates processes linked to cellular survival, extracellular matrix and adhesion molecule signaling but also metabolic processes, e.g. via the PI3K/AKT pathway." I have doubt in the final part "PI3K/Akt pathway" because it is not the downstream signal molecule for FGFs. Please put a citation for this section. 2. Endoplasmic reticulum appears to be more common usage. Please change the word "Endoplasmatic" into "Endoplasmic". 3.Chiara Degirolamo et al. has published a review about the therapeutic potential of FGFs in Nature Reviews Drug Discovery (2015). Some FGFs therapeutics under clinical trails are not described in this manuscript. Authors could update the content in the section of "FGF signaling as a novel drug target in NAFLD and NASH"

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