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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 49448

Title: Gut-liver axis signaling in portal hypertension

Reviewer's code: 00031629

Position: Editorial Board

Academic degree: FACG, FCPS, MD, PhD

Professional title: Professor

Reviewer's country: Pakistan

Author's country: Austria

Reviewer chosen by: Ruo-Yu Ma

Reviewer accepted review: 2019-06-25 03:22

Reviewer performed review: 2019-06-25 04:07

Review time: 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] 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[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced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

Interesting topic and very well written minor English language polishing is required

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 49448

Title: Gut-liver axis signaling in portal hypertension

Reviewer's code: 02903574
Position: Peer Reviewer
Academic degree:
Professional title:
Reviewer's country: Switzerland
Author's country: Austria

Reviewer chosen by: Ruo-Yu Ma

Reviewer accepted review: 2019-06-04 06:32

Reviewer performed review: 2019-06-25 04:23

Review time: 20 Days and 21 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
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
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[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
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SPECIFIC COMMENTS TO AUTHORS

In this review, Simbrunner et al. aim at providing a wide overview of the evidence

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linking the gut and the liver in the pathogenesis of chronic liver disease. The authors should be congratulated for a tremendous amount of work they did at compiling >150 references, and for the overall quality of the redaction. Moreover, it is a hot topic, so it is of interest. That said, there are important limitations to this work General comments: - The fact that this is a narrative review raises important limitations: in fact, without a systematic approach, the reader is obliged to believe the authors in the formulation of their points (it is highly likely that publications with positive results are more easily cited in this word compared to negative, or counter-intuitive data, which also exist in this topic). --> While it seems impossible to re-design the review with a systematic approach, this is a serious limitation of the current work, and it should be acknowledged. --> Even though it is not a garantee for quality, a "box" or a short paragraph describing how and from where the cited studies where assessed for this review, would be of use. See for example the Lancet narrative review articles, with such a box. - A very important question in interpreting the role of the gut-liver axis in the pathogenesis of chronic liver disease is the "chicken-egg" question, as noticed by the authors. While the reader hopes to find answers to this question in discovering the manuscript, the authors fail to provide a clear opinion on that matter (as exemplified by the conclusion of the manuscript, which points out again the chicken-egg question. - This review would be improved by even a short paragraph summarizing the important evidence linking the gut-liver axis and the incidence of hepatocellular carcinoma. In fact, hepatocarcinogenesis is one of the well documented situation where the gut liver axis has an impact. To this end, a relevant study to this topic should be cited (J Hepatol. 2018 May;68(5):978-985) - A lot (not all) of the evidence summarized here is quite oldish now (especially regarding the first part of the manuscript on portal hypertension). This criticism does not apply to the last paragraphs of the manuscript where recent data are interestingly summarized. In other words. this manuscript does not add a lot to the

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debate. - The review is much too long and disorganized. The overwhelming abundance of the developped arguments makes it, honestly, not a pleasure to read. The authors should make their review more concise, by cutting some parts (especially in the first part of the manuscript on portal hypertension). Specific comments: --> Regarding the Paragraph "Gut-liver crosstalk influences immune system homeostasis": - This paragraph deserves improvement: The sentence "The physiological slow blood flow in liver sinusooids enables [...] immune cells" lacks a reference. Please cite what you discuss. The same point is valid for the sentence just after that ("Additionally, fenestrations [...]"), and another sentence later ("As a result, additional monociyte-derived macrophages, but also natural killer [...]". Cite accordingly to what you have read in the literature. - This paragraph also deserves adding a sentence or two on the very important mechanism that is endotoxin tolerance. Indeed, much more than common bone-marrow-derived antigen presenter cells (such as monocytes and dendritic cells) Kupffer cells are capable, upon binding LPS on TLR4, of mitigating chronic inflammation by adopting an immunomodulatory phenotype and by reducing their antigen-presentation capacity. --> Regarding the Paragraph "Intestinal permeability is affected by portal hypertension": The author should specify on which species is based the study[56] that they summarized the results of. "an animal study" is a blunt formulation, and just saying whether it was mice or other would just make more sense. The abbreviation PSC should be introduced in the paragraph "In an animal model of primary sclerosing cholangitis [...]". - Reference 130 did not work on endnote. --> Regarding the Paragraph "Bile acids: communicators between liver and gut": This paragraph deserves some more work. Indeed, it is quite awkward to summarize a whole paragraph by citing a single reference. Than it seems that you are summarizing a study, not a whole concept developped through a whole paragraph. - The sentence specifying that FGF19-FGFR4 interaction depens on either aKlotho of Bkotho is of no use to this manuscript, and it does not

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provide a clear statement (aKlotho or bKlotho, ok but what should I keep). Considering that the manuscript is already so long, I would take the opportunity to remove this sentence. - Figures: While the legend is clear, the design of Figure 1 does not show clearly (nor explains how) FXR agonism protects from bacterial translocation. Arrows indicating increased expression of TJ proteins (and other mechanisms) would be of use. Figure 2 is confusing. The legend states that FXR-FGF 19 signalling [...] affects fibrosis and inflammation via HSCs and liver-resident macrophages. But the main text barely provides evidence surrounding such an argument. Moreover, TNFa, IL1b and IL-6 are all symbolized with the same red triangle which appears to bind the same receptor. But these cytokines are different in their structure, and bind different receptors. Therefore this figure is overly reductory. Overall, there are far too many abbreviations in the figure legends, and even though the key is given for each figure, it takes a lot of time to understand the figure. In other words, figures are not of a big help to this manuscript. The table summarizing the evidence regarding therapeutic approaches is usefull, but the side effects of drugs such as OCA should also be reported because they appear to be common.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 49448

Title: Gut-liver axis signaling in portal hypertension

Reviewer's code: 03883459
Position: Peer Reviewer
Academic degree: PhD
Professional title: Senior Postdoctoral Fellow
Reviewer's country: Italy
Author's country: Austria

Reviewer chosen by: Ruo-Yu Ma
Reviewer accepted review: 2019-06-25 09:33
Reviewer performed review: 2019-06-28 08:38
Review time: 2 Days and 23 Hours

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	[Y] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
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[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

This is an interesting review, investigating the impact of portal hypertension on the

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gut-liver axis by providing both insight into pathophysiology and clinical observations, as well as therapeutic strategies in advanced chronic liver disease. The review also suggests treatment strategies targeting the gut-liver axis via modulation of microbiota composition and function. This is a well-prepared manuscript, adding valuable information on our understanding of liver complex pathogenetic mechanisms involving microbiota. The abstract well summarize and reflect the work described in the manuscript, the background and the discussion are coherently organized.

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