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To
Editorial Board
World Journal of Gastroenterology

Vienna, 14-Aug-2019

Re: Revised Manuscript (BPG Manuscript Nr 49448)

"Gut-liver axis signaling in portal hypertension"

Dear Editorial Board of WJG,

We have received the excellent comments of the Editors and the reviewers on our manuscript. Thank you for the opportunity to provide you with a response and to submit a revised version of our manuscript. We addressed all issues raised and worked on additional improvements of the manuscript. The most relevant add-ons and changes of the revised version can be summarized as following:

- Improvement of organization and structure of the manuscript
- Revision of the figures according to the editor's and reviewer's comments and instructions
- Dedicated subsection towards genetic and experimental studies to address the "chicken vs egg" conundrum

Please find our revised version of the manuscript attached and a point-by-point response below. We are looking forward to your evaluation of our revised manuscript.

With best regards,

Dr. Benedikt SIMBRUNNER *Prof.PD.Dr.Thomas REIBERGER*

Editorial comments:

1) *Please provide language certificate letter by professional English language editing companies (Classification of manuscript language quality evaluation is B).*

We appreciate the high standards of the World Journal of Gastroenterology in regard to the linguistic quality of the manuscripts accepted in your journal. However, in our case, we (the authors) all have undergone extensive English language classes in High School and College, as well had dedicated courses on "Scientific English" at the Medical University of Vienna during Medical School. Two authors, i.e. Prof. Dr. Thomas Reiberger and Prof. Dr. Michael Trauner have attended renowned Medical Schools and University Hospitals in the United States for several years. Prof. Reiberger has spent 3 years at Harvard Medical School and Massachusetts General Hospital in Boston and has certainly acquired profound English language skills that qualify him to publish in international journals without an additional certificate.

The manuscript has been carefully proofread by all coauthors all of whom have published several original articles and publications and reviews in top-ranked international journals. None of these articles has ever been rejected or criticized due to inadequacy of the manuscripts' English language quality. Furthermore, no specific comments towards language errors have been made by any of the reviewer.

We want to assure the editors that we have taken this request very seriously and have repeatedly proofread our revised manuscript and optimized English language expression wherever possible.

Thus, we kindly ask you for reconsideration of the necessity to provide a costly professional English language quality certificate by a company, which would create additional unforeseen costs for which no financial support or grant support is available. If you have any doubt that our revised manuscript lacks sufficient quality in English language, please indicate the page numbers/paragraphs and we will re-evaluate our statement.

2) *Audio core tip: In order to attract readers to read your full-text article, we request that the author make an audio file describing your final core tip, it is necessary for final acceptance. Please refer to Instruction to authors on our website or attached Format for detailed information. The accepted formats are mp3 or wma.*

We have provided the audio file in mp3 along with the other uploaded files on the system.

3) *Please provide the decomposable figure of all the figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as "Manuscript No. -*

image files.ppt" on the system. Make sure that the layers in the PPT file are fully editable. For figures, use distinct colors with comparable visibility and consider colorblind individuals by avoiding the use of red and green for contrast.

We have uploaded the figures in a power point file as requested. The layers and components are movable and editable. We have avoided red and green colors in order to improve contrast.

4) *Your manuscript should be prepared with Word-processing Software, using 12 pt Book Antiqua font and 1.5 line spacing with ample margins.*

Thank you for indicating the required style specifications, we have adapted the font and font size, line spacing and ample margins as requested.

5) *Please revise and perfect your manuscript according to peer-reviewers' comments. Please upload the required files on the system.*

We have adapted and revised the manuscript according to the reviewer's comments and are gladly providing the revised manuscript along with the other required files via the online system.

Reviewer comments:

Reviewer #1

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

We thank the reviewer for evaluating our manuscript and for finding interest in our review. In regard to the required language polishing, we made sure to carefully and repeatedly proofread our revised manuscript and made necessary corrections in order to optimize Scientific English language expression. However, if the reviewer finds that we have missed any specific inaccuracies in regard to the linguistic quality of our manuscript, we will be happy to correct them accordingly.

Reviewer #2

General comments:

1) 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.

We thank the reviewer for raising this important issue and acknowledge the limitations of a "narrative" review style. We appreciate the aspects of systematic reviews that may limit the selection bias towards positive results. However, we have put serious effort into a fair evaluation of the available evidence and published original data, and finally decided to use a narrative style for the reader in order to acquire the current "point-of-view" on the relevance of gut-liver-axis signaling in portal hypertension.

In any case, we have tried to thoroughly evaluate quality and relevance of the existing literature presented in this review and hope that our revised work can be perceived as a comprehensive summary of the current state of knowledge that may be helpful to basic as well as clinical scientists, since an important aim of our work was to interface with laboratory and clinical data.

Since we still agree with the reviewer that the "narrative" style of this review represents a potential limitation, we have included a respective statement on the narrative style of our review and associated limitations in our revised manuscript:

"While this review aims to comprehensively summarize the current state of knowledge obtained by experimental and clinical studies, it is designed as a narrative review. Thus, the possibility of selection bias and underreporting of negative studies represents a potential limitation of this review."

--> 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.

The reviewer gives an important example how the approach towards literature research is displayed in narrative reviews published in top-ranked journals such as Lancet. We have searched for examples in Lancet narrative reviews and have added a text box summarizing the strategy for systematic literature search strategy and for selection of articles/references to the revised manuscript:

"We searched for manuscripts in PubMed and Scopus databases using the search terms "portal hypertension", "cirrhosis", "bacterial translocation", "PAMP(s)" or "DAMP(s)", "intestinal barrier", "vascular barrier", "inflammation" and "FXR" alone or in combination to identify relevant manuscripts. All article types available in English language were considered and assessed for thematic relevance and quality, while priority was given to publications from the past 5 years. Furthermore, we searched for randomized trials on clinicaltrials.gov that were either ongoing or recently completed as well as recent abstracts from major international conferences. The references that were finally included were selected in consideration of their novelty and relevance to pathophysiological concepts."

2) 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.

We appreciate this important comment by the reviewer, calling for distinct conclusions derived from the presented data in this review. In our opinion, the "chicken-egg" conundrum still has not been entirely solved to date – although there exist mechanistic studies that link e.g. bacterial translocation to an advanced state of liver disease. Still it seems difficult to divide whether bacterial translocation promotes progression of liver disease or is rather caused by progression of liver disease. RCTs testing therapeutic interventions would be a viable option to address this question, however, as discussed in our manuscript, e.g. clinical trials in patients testing treatment with antibiotics or FXR agonists have not (yet) provided conclusive data in this regard.

To address this dilemma, we have chosen an inventive approach and presented data from studies focusing on the role of genetic polymorphisms in advanced chronic liver disease. Impact of genetic polymorphisms that impact on signaling pathways involved in intestinal barrier or bacterial translocation do not leave us with the question "cause or consequence of disease progression" since this particular genetic condition is inherently

present in affected patients. To our knowledge, this is the first review on portal hypertension and its role in the gut-liver axis that addresses this field of research.

Furthermore, we have presented data from Geerts et al. who found that macrovascular leakage of macromolecules was only observed in BDL (cirrhosis and portal hypertension) as compared to PPVL (portal hypertension but no underlying liver disease) rats [1]. Additional relevant data were recently (i.e. during the time of peer review of this manuscript) published by Sorribas et al. who concluded that the muco-epithelial and the gut-vascular barrier and, ultimately, bacterial translocation was profoundly impaired in cirrhotic mice (induced by bile duct ligation, BDL or carbontetrachloride administration, CCl4) while this effect was not present (or at least significantly less pronounced) in portal-hypertensive mice without cirrhosis (partial portal vein ligation, PPVL) [2]. Since we think that this publication deserves attention and may represent an important puzzle piece towards solving the "chicken-egg" question we have included it in our revised manuscript:

"Interestingly, Sorribas et al. recently found that the gut-vascular and mucosal epithelial barriers were profoundly impaired in cirrhotic mice (induced by BDL or carbontetrachloride administration, CCl_4) while this effect was not present, or at least significantly less pronounced, in portal-hypertensive mice without cirrhosis (PPVL) [2]. Importantly, it was observed that these barriers were regulated by FXR-dependent mechanisms, and BT was reduced upon treatment with FXR agonists [2].

These experimental data are highly relevant for the "chicken vs. egg" debate because they suggest that portal hypertension itself has only a minor impact on barrier integrity, while it also explicitly considers that the muco-epithelial and gut-vascular barrier are different entities. Along with observations from genetic studies that suggest that BT and inflammation do not only result from decompensation but rather are drivers of (further) hepatic decompensation, efforts towards elucidating this conundrum have the potential to identify therapeutic approaches in patients with cirrhosis and portal hypertension."

3) *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)*

The reviewer makes an excellent point by stating that the link between hepatocellular carcinoma (HCC) and the gut-liver axis should be mentioned in this review and gives an example of an exceptional experimental study that was published recently. We have included a paragraph that is dedicated to the impact of gut-liver axis signaling and hepatocarcinogenesis in our revised manuscript:

"The significance of gut-liver crosstalk is further emphasized by studies that demonstrate a connection between HCC development and tumor progression to chronic hepatic inflammation caused by BT [3]. For example, TLR activation by LPS promotes not only fibrosis but also hepatocarcinogenesis [4, 5], while blockade of the TLR4 signaling cascade reduced HCC formation [6, 7]. Orci et al. recently investigated the role of TLR4-mediated pathways in HCC recurrence in mice that underwent temporary clamping of portal vessels to induce ischemic liver injury. The resulting obstruction of splanchnic blood flow resulted in increased BT and promotion of HCC recurrence *via* TLR4 signaling pathways. Importantly, ischemic preconditioning, intestinal decontamination and interference with TLR4 signaling impeded tumor recurrence [8]."

4) *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 debate.*

We appreciate the reviewer's comment, suggesting to re-evaluate whether the data presented in this review are up to date. However, we want to express our opinion that, although some presented data/studies (predominantly in the first parts of our manuscript) might seem "oldish" by means of publication date, these references still represent critical literature on methodically sound and thematically highly relevant studies that contain important information. These studies provide the ground for the subsequent section of our manuscript (i.e. focused on the gut-liver axis concept) and we rely on them to draw a complete (historic) picture of the topic in our review article. As the reviewer mentioned, the last parts of our manuscript report more recent data.

Still we acknowledge the reviewer's criticism and thus, we have reduced the length of our revised manuscript and have omitted some older references. We hope that the reduced number of potentially redundant references in the revised review article are within the desired limit.

5) *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).*

We regret that the reviewer was not pleased with the organization and length of our manuscript. The reviewer's feedback is highly appreciated, and we have re-evaluated the structure of our manuscript and identified potentially redundant sections, sentences, and paragraphs that were shortened or deleted from the revised article.

Ultimately, we have reduced the length of our revised manuscript and optimized the organization/structure of the manuscript. Data on genetic polymorphisms as well as

recent experimental data that are important towards solving the "chicken vs egg" dilemma were summarized in a new subsection that is dedicated to this issue. This should enhance the reader's attention to this important topic as well as meet the reviewer's suggestion that we need to address this ongoing discussion more distinctly. Additionally, we have moved sentences/paragraphs that were thematically misplaced to other subsections or removed them from the manuscript if abundant. These changes make the revised manuscript more concise.

Specific comments:

--> *Regarding the Paragraph "Gut-liver crosstalk influences immune system homeostasis":*

6) 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.

We are thankful for this comment and have cited the respective references accordingly in our revised manuscript.

7) *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.*

We appreciate this exceptional comment by the reviewer that endotoxin tolerance deserves attention. Since the length of the manuscript has already been criticized, we have tried to concisely summarize endotoxin tolerance in our revised manuscript, while citing a recently published review that is solely dedicated to this mechanism:

"For example, chronic exposure to LPS can induce endotoxin tolerance by TLR4 dependent pathways, which is characterized by dampened antigen presentation, reduction of proinflammatory mediators and overexpression of anti-inflammatory signaling molecules [9]."

--> *Regarding the Paragraph "Intestinal permeability is affected by portal hypertension":*

8) 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 [...]".

We agree that information towards the specific animal species that were used in the cited studies should be given in the text and have corrected the respective sentences in our revised manuscript:

"An experimental study comparing two rat models of PHT, partial portal vein ligation (PPVL) and common bile duct ligation (BDL), demonstrated that angiogenesis in the splanchnic vessels is increased in both models, as assessed by microvascular density in intravital microscopy and the endothelial marker CD31 [1]. Similarly, vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS) were elevated in PPVL and BDL rats."

Furthermore, we have introduced the abbreviation PSC in the respective paragraph as pointed out by the reviewer.

9) Reference 130 did not work on endnote.

We thank the reviewer for indicating this error, we have removed the faulty link and inserted the appropriate reference.

--> Regarding the Paragraph "Bile acids: communicators between liver and gut":

10) 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.

We are sorry, but we could not confirm that we had only a single reference for our paragraph on "bile acids: communicators between liver and gut". Indeed, we had used about 30 new references (#128-#162) to underline the statements given in the respective article. Please advance us, if there are specific facts where we missed to indicate adequate references.

11) The sentence specifying that FGF19-FGFR4 interaction depens on either aKlotho of Bkotho is of no use to this manuscript, and it does not 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.

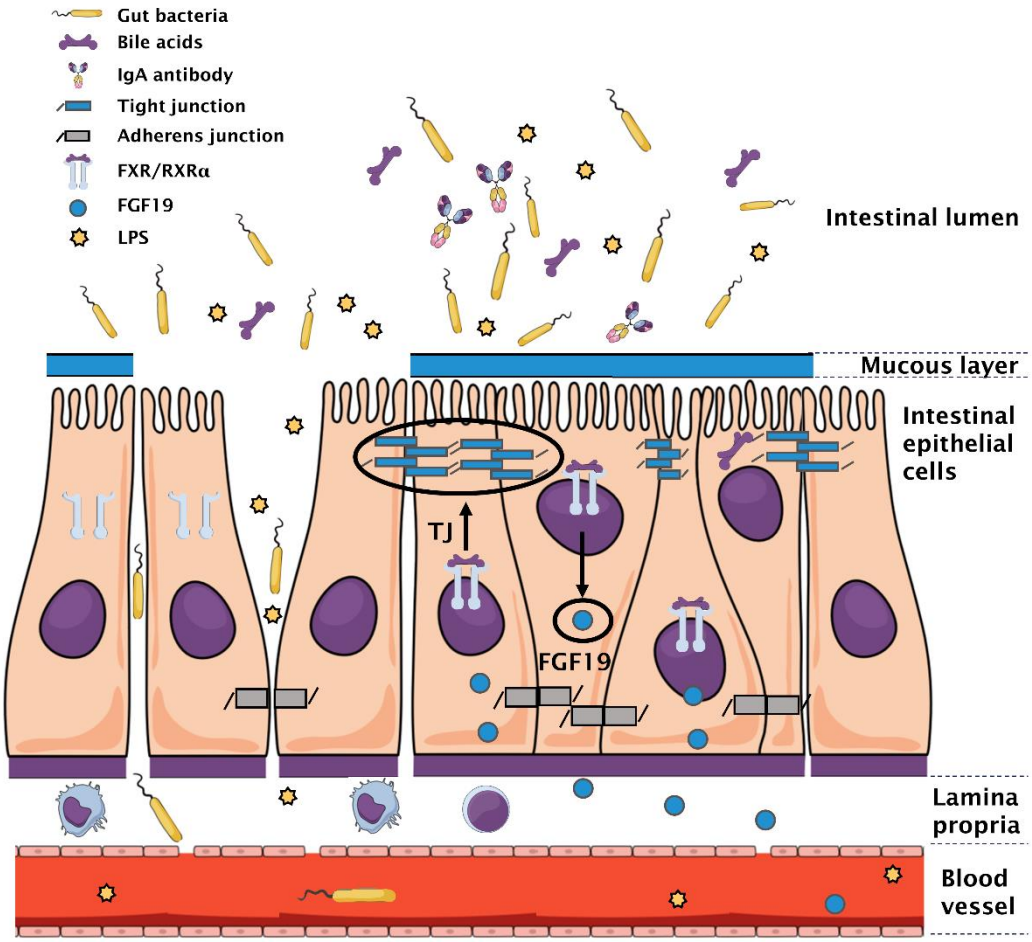
We thank the reviewer for this suggestion, we have removed the sentence in our revised manuscript.

Figures:

12) 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.

The reviewer makes an important point that FXR-dependent upregulation of tight junction proteins should be clearly visualized in this figure, as well as other mechanisms e.g. transcription of FGF19. We have inserted arrows and circles that indicate these mechanisms in our revised figure. Furthermore, we have followed the editor's request to avoid red and green for contrast. In this process, we have unitized the color of figure components that are regulated by FXR, hoping that this will be perceived as an additional visual improvement of the figure's comprehensiveness:

"Figure 1. An impaired mucosal epithelial barrier integrity facilitates bacterial translocation and is regulated by farnesoid X receptor-dependent mechanisms."



"Increased systemic inflammation in cirrhotic patients as compared to healthy subjects is considered to be associated with intestinal dysbiosis leading to translocation of pathogens – or derived pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) – into the portal circulation, which is further facilitated by an impaired intestinal barrier. Farnesoid X receptor (FXR) activation in ileum enhances the expression of Fibroblast Growth Factor (FGF) 15 (mice) or 19 (humans) *via*

binding to response elements in the nucleus. FXR activation leads to upregulation of tight junction proteins and decrease of bacterial translocation.

Abbreviations: FXR = farnesoid X receptor; IgA = Immunoglobulin A; RXRα = retinoid X receptor; FGF = fibroblast growth factor; LPS = lipopolysaccharide; PAMPs = pathogen-associated molecular patterns; DAMPs = danger-associated molecular patterns; TJ = tight junction."

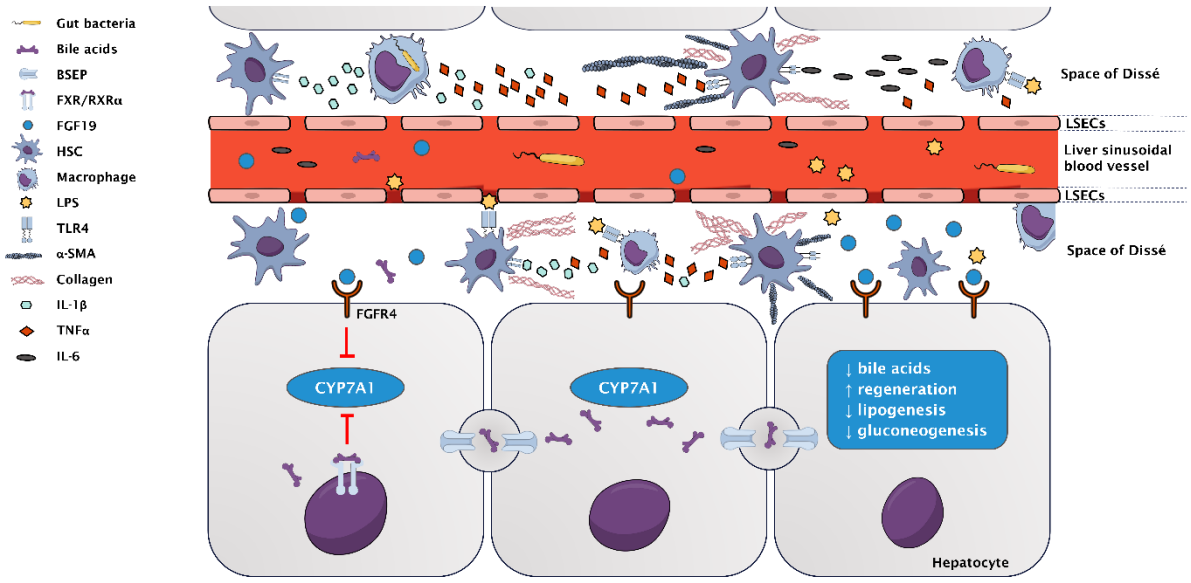
13) Figure 2 is confusing. The legend states that FXR-FGF 19 signalling [...] affects fibrosis and inflammation via HSCs and liver-resident macrophages. But the main text barely provides evidence surrounding such an argument. Moreover, TNFa, IL1b and IL-6 are all symbolized with the same red triangle 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.

We agree with the reviewer that the current state of knowledge does not provide evidence that FXR-FGF19 signaling directly induces "fibrosis and inflammation". Thus, we have the impression that the figure title may have been misunderstood due to a suboptimal sentence structure: we have meant to state a) FXR-FGF19 signaling between gut and liver regulates bile acid homeostasis and b) bacterial translocation affects fibrosis and inflammation via hepatic stellate cells and liver-resident macrophages. Both statements are delineated in figure 2 and were elaborated in the main text.

We find this comment by the reviewer very important and agree that the sentence structure of our figure title might have been unclear. Thus, we have revised the title accordingly. Additionally, we have adapted the figure title as instructed by the editorial office ("Please don't include abbreviations in the title of the figure/table"):

"Figure 2. Farnesoid X receptor-Fibroblast Growth Factor 19 signaling between gut and liver regulates bile acid homeostasis and impacts on mucosal barrier function. Bacterial translocation triggers fibrosis and hepatic inflammation *via* activation of hepatic stellate cells and liver-resident macrophages."

The criticism towards the presentation of TNFa, IL1b and IL-6 and receptors with the same graphical design has been well perceived. We want to assure the reviewer that we are aware of structural differences of both cytokines and receptors, however, we had chosen to summarize these molecules by just one design while we are aware that all of them have distinct function while they universally represent proinflammatory cytokines involved in signaling between macrophages/Kupffer cells and hepatic stellate cells [10]. Thus, we had intended to avoid an overload of different figure elements. In any case, the reviewer's feedback is highly appreciated, and we revised the figure by assigning different designs to cytokines and receptors:



"Fibroblast Growth Factor (FGF) 19 binds to FGF receptor 4 (FGFR4) on hepatocytes which subsequently suppresses the expression of CYP7A1. FGF19 is upregulated postprandially and influences Farnesoid X receptor (FXR)-dependent metabolic pathways involved in gluconeogenesis, protein synthesis, insulin sensitivity and lipid profile. Kupffer cells and monocyte-derived macrophages produce cytokines and chemotactic molecules in response to liver injury. Recognition of lipopolysaccharide (LPS) by toll-like receptor (TLR) 4 on macrophages and Kupffer cells results in activation of the NFκ-B-regulated inflammasome and increases tumor necrosis factor (TNF)-α synthesis. In the continuous presence of injury, pathogen-associated molecular patterns (PAMPs) and/or danger-associated molecular patterns (DAMPs), these cells create a proinflammatory environment that finally cause hepatocyte injury and fibrosis *via* hepatic stellate cell (HSC) stimulation that results in production of collagen and α-smooth muscle actin (α-SMA).

Abbreviations: FXR = farnesoid X receptor; RXRα = retinoid X receptor; BSEP = bile salt export pump; FGF = fibroblast growth factor; FGFR4 = fibroblast growth factor receptor 4; LPS = lipopolysaccharide; α-SMA = α; TNF = tumor necrosis factor; IL = interleukin; HSC = hepatic stellate cell; LSEC = liver sinusoidal endothelial cell."

14) 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 criticism towards abbreviations in the figure legends has been raised by the editorial office as well, who gave us specific instructions to correct the figure legends: "Please explain all the abbreviations in the figure/table legends as full name (abbreviation)".

Hence, we have adapted the figure legends accordingly in our revised manuscript.

15) 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.

We agree with the reviewer that the side effects of drugs such as OCA should be reported in this review, since this may pose as an important clinical issue that significantly limits the applicability of these drugs.

Therefore we have explicitly mentioned that side effects were frequently reported in trials of OCA in humans and also underlined the major importance of pruritus as a serious and treatment-limiting side effect in the table of our revised manuscript:

a) **"The FLINT RCT in non-cirrhotic NASH patients indicated that OCA improves histological features of the disease, however, pruritus seems to be an inconvenient side effect that was reported by approximately one fifth of patients [11]. Furthermore, unfavorable changes in the lipid profile (increase of total and LDL cholesterol) were observed upon OCA treatment [11]. In two RCTs in PBC patients, OCA improved serum levels of transaminases and bilirubin, however, side effects like pruritus were also more frequent in the treatment groups as compared to placebo [12, 13]."**

b) **Table:**
"OCA/NASH/NCT01265498: improved histological features; 20% pruritus, impaired lipid profile [11]"
"OCA/PBC/NCT01473524: improved biochemical laboratory values; frequent pruritus [12, 13]"

Reviewer #3

1) *This is an interesting review, investigating the impact of portal hypertension on the 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.*

We thank the reviewer for evaluating our manuscript and for finding interest in our review. In regard to the required language polishing, we made sure to carefully and repeatedly proofread our revised manuscript and made necessary corrections in order to optimize Scientific English language expression. However, if the reviewer finds that we have missed any specific inaccuracies in regard to the linguistic quality of our manuscript, we will be happy to correct them accordingly.

References used in this response letter:

1. Geerts, A.M., et al., *Increased angiogenesis and permeability in the mesenteric microvasculature of rats with cirrhosis and portal hypertension: an in vivo study.* Liver Int, 2006. 26(7): p. 889-98.
2. Sorribas, M., et al., *FxR-modulates the gut-vascular barrier by regulating the entry sites for bacterial translocation in experimental cirrhosis.* J Hepatol, 2019.
3. Yu, L.X. and R.F. Schwabe, *The gut microbiome and liver cancer: mechanisms and clinical translation.* Nat Rev Gastroenterol Hepatol, 2017. 14(9): p. 527-539.
4. Dapito, D.H., et al., *Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4.* Cancer Cell, 2012. 21(4): p. 504-16.
5. Seki, E., et al., *TLR4 enhances TGF-beta signaling and hepatic fibrosis.* Nat Med, 2007. 13(11): p. 1324-32.
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9. Liu, D., et al., *Recent advances in endotoxin tolerance.* J Cell Biochem, 2019. 120(1): p. 56-70.
10. Tilg, H. and A.M. Diehl, *Cytokines in alcoholic and nonalcoholic steatohepatitis.* N Engl J Med, 2000. 343(20): p. 1467-76.
11. Neuschwander-Tetri, B.A., et al., *Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial.* Lancet, 2015. 385(9972): p. 956-65.
12. Nevens, F., et al., *A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis.* N Engl J Med, 2016. 375(7): p. 631-43.
13. Kowdley, K.V., et al., *A randomized trial of obeticholic acid monotherapy in patients with primary biliary cholangitis.* Hepatology, 2018. 67(5): p. 1890-1902.