

Objective: Answering Reviewers

Title: The starring role of TLR-4 activation in gut-liver axis

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- Responses to the Editor comments:

- 1) The title might be changed to 'The Starring Role of TLR4 in the Gut Liver Axis'.

Response: The title has been changed accordingly

- 1) The abstract on page 2 should be revised (see attached PDF).

Response: The abstract and the entire manuscript have been revised according to suggestions proposed by you in the attached PDF

- 2) Many grammatical and repetitive phrases (e.g. evidences) were suggested to be different starting in the introduction.

Near and far organ systems – changed to local and remote organ systems.

The section on dysbiosis in liver disease and cirrhosis is interesting and important but is in particular need of re-writing.

Response: The introduction and the section on dysbiosis have been amended and reported errors corrected.

- 3) Page 7 'cytokines' are described in para 1, which ones and what is the role of nitric oxide? Both are important, can they be more extensively developed?

Response: The main cytokines are now mentioned in the text. Some of them have been further discussed in the following paragraphs.

- 4) Page 8. Mediators modulating gut motor function e.g. cytokines and the relationships to prostanoids, can be described. At the end of para 1, please consider looking a Al-Kofahi et al., 2015 which has some relevance to intestinal smooth muscle contractility and inflammation (Al-Kofahi M, Becker F, Gavins FN, Woolard M, Tsunoda I, Wang Y, Ostanin D, Zawieja DC, Muthuchamy M, von der Weid PY,

Alexander JS. Interleukin-1 beta Reduces Tonic Contraction of Mesenteric Lymphatic Muscle Cells: Involvement of Cyclooxygenase-2 / Prostaglandin E2. Br J Pharmacol. 2015 May 18. doi: 10.1111/bph.13194.).

Response: The requested issues are now inserted in the section as well as the suggested reference.

- 5) Page 9, section on junctional proteins is interesting, which proteins are involved? So much emphasis is placed on barrier, permeability, etc. what about junctional organization? Also this page, could authors be specific when describing TLR2.

Response: Tight junctions proteins and their organization are now more extensively discussed and TLR2 description has been expanded.

- 6) Page 10 -section on miRNAs. This section gets very dense and would benefit from more interpretation of the significance of these mediators in gut liver axis.

Response: Section on miRNAs has been simplified with shorter sentences and clearer content

- 7) Page 11. Good, but needs stylistic revision, English language revision.

Response: English language has been revised

- 8) Page 12. Discussion on CXCR4- please clarify top paragraph.

Response: Paragraph regarding CXCR4 has been clarified

- 9) Conclusion section. Can this section be more specific and possibly re-integrate the different sections which make up the study creating a smoother summary of the authors conclusions regarding the clinical significance and applications of these findings/

Response: Conclusions have been re-written integrating the different sections and focusing on the clinical significance and application of the reported findings.

- **Responses to Reviewers comments:**

Reviewer 00037575

General comments: The manuscript's subject is interesting and pertinent for the journal. Minor revisions as suggested will improve its readability. Minor comments: The manuscript should be reviewed for stylistic, omissions (e.g. meaning of the abbreviations used), typos and grammar errors. Abbreviations such as NAFLD on

page 2 should be explained in the text when first used even if added in the “list of abbreviations”, and then again in Figure 2 – NAFLD and NASH - such that the figure can stand alone. Example of abbreviations that should be explained when first used in the text (and eventually added to the “list of abbreviations”) includes LSECs and PCDC4, among others.

Response: Meaning of the abbreviations used are now specified both in the text and in the list of abbreviations. Stylistic revision was done and typos and grammar errors corrected. NAFLD is now explained in the text when first used and then again in Figure 2 together with NASH. LSECs and PCDC4 are also explained.

Reviewer 02446669

The manuscript is focused on an interesting topic. The figures nicely summarized the information. However, major revision of the text is needed since there are grammar and style mistakes, and similarities with phrases from other previously published papers.

Response: The text has been extensively revised in order to amend it from grammar and style mistakes. Similarities with phrases from other previously published papers have been now modified and sources properly cited.

Reviewer 00503257

It is nice to be more concisely writing style. More detailed description regarding TLR4 signaling pathways should be added.

Response: A more detailed description regarding TLR4 signaling pathways has been added on page 11. The change is underlined.