

Name of Journal: World Journal of Immunology

Manuscript Type: OPINION REVIEW

Type: Invited manuscript ID

Dear Editor,

Dear reviewers,

Thank you for your time to revise our Manuscript: The interactions between human microbiome, liver diseases, and immunosuppression after liver transplant

Authors: Peruhova M, Sekulovska-Peshevska M and Velikova T.

We have incorporated the suggestions made by the reviewers. Those changes are highlighted within the manuscript. Please see below, in blue, for a point-by-point response to the reviewers' comments. All page numbers refer to the revised manuscript file with tracked changes.

Reviewer #1

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Peruhova et al. spotted the interactions between human microbiome, liver diseases, and immunosuppression after liver transplants. The opinion review is well written and highlights an important issue in the field. The title reflects the main subject of the manuscript. The abstract reflects the work described in the manuscript. The keywords reflect the focus of the manuscript. The manuscript appropriately cites the latest and important references. Language is acceptable but needs some revision.

- Thank you for the overall evaluation of our paper. We have revised the language to make it clearer and concise.

Minor points:

- No explicit differentiation between the two terms, microbiome and microbiota was given. Therefore, short definitions should be given.

- We appreciate your constructive comments. We have added additional information following your suggestion. We gave a short definition for these two terms.

- Some definitions should be given; e.g., dysbiosis

- We have additionally define the condition dysbiosis.

- Some language corrections are needed: e.g. Page 5, second paragraph, last line: evaluated..... Correct to evaluate Page 6, second paragraph, last line: maintain..... Correct to maintaining

- Thank you for your insightful comments. We corrected the language mistakes in the text as you recommended.

- Page 4, third line: a reference should be added to the data mentioned above

- We agree with the referee and added the reference #4.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Minor revision

- Thank you for the feedback and comments on our paper.

Specific Comments to Authors: Review of manuscript ID: 68033 Title: The interactions between human microbiome, liver diseases, and immunosuppression after liver transplant Summary: In this review, Peruhova M et al. look at the interaction between the immune system and the microbiome following LT. They further review the impact on microbiome on de novo malignancy.

Comments to the authors: 1. Focus – I think the authors should focus on the microbiome and LT. After the introduction, you can discuss “Immunosuppressive therapy and microbiota after liver transplant.” You can then discuss “Allograft rejection and microbiome.” You can then have a section on complications following transplant and include de novo/recurrent HCC and if there are enough studies you could include a section on metabolic syndrome. As you note, CVD and malignancy are the most common causes of death post LT. The small section on liver disease should be removed.

➤ Thank you for the valuable comments. We did our best to focus on microbiome and LT, as the title states. Regarding the section “Immunosuppressive therapy and microbiota after liver transplant”, we had published recently immunosuppression in LT paper (available here <https://www.mdpi.com/2036-7422/12/3/25>). However, we added such paragraphs, including on allograft rejection and microbiome. The above-mentioned paper contains also de novo tumors in patients on immunosuppressant drugs after LT.

2. Introduction – move the 3 paragraphs to above the 2nd. This is where you can add dysbiosis/overgrowth may lead to disease. You can also include how the microbiome differs in patients with good health and liver disease. What about microbiome post LT?

- ✓ We took in consideration your opinion about the structure of the article. We rearranged the paragraphs as you recommend.
- ✓ Thank you for valuable remark. We made a few changes according to your suggestions. The rest of them are well written in section: human microbiome and hepatocellular carcinoma.

3. Human microbiome and liver disease – specify which protective bacteria are decreased (eg. Lachnospiraceae) and which pathogenic bacteria are increased. Include this information in the introduction. I do not think you need to include Sataphaty study. 4. Make a section on HCC and keep the 2nd and 3rd paragraphs of the Human microbiome and liver disease section.

- ✓ We are grateful for the important note. We removed the section Human microbiome and liver disease, and we made a section Human microbiome and hepatocellular carcinoma.

5. Allograft rejection and microbiome - can you expand on how the microbiota and immune system influence each other? Eg. the microbiome helps develop the immune system by providing microbial metabolic products. The immune system affects the microbiome ...

- Thank you for the valuable note. We have added this section.

6. Rat models (ref 14) – expand on what changes were seen. How did these changes help predict rejection?

- We have cited the proper citation. We have expanded the paragraph.

7. Immunosuppressive therapy and microbiota after LT – first sentence; do you mean avoidance of rejection after LT depends primarily on IS? Some studies suggest IS may impact PSC recurrence, but there is no clear cut evidence. Similarly NASH recurrence is common, but I do not believe studies have shown impact of IS.

- We agree completely with the referee's opinion.

8. Immunosuppressive therapy and microbiota after liver transplant – I think you should remove the 2nd paragraph. It should be in the de novo malignancy/HCC section.

- We agree completely with the referee. We have cited our paper on de novo mutations after LT.

9. Immunosuppressive therapy and microbiota after liver transplant – add studies on cyclosporine (Liver Transpl. 2003; 9:484–488.) and sirolimus (PLoS One.

2012;7:e41584.) to complete the section. Minor comments: 1. Sentence – “In addition, toll-like receptor 4 activation in HCC lines with lipopolysaccharide causes the epithelial-mesenchymal transition.” You are missing the word cell; HCC cell lines. 2. It would be beneficial to get an individual proficient in English to edit the manuscript.

✓ We appreciate your constructive comment. We made the necessary corrections.