

From:

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To:

Patras, 8 November, 2022

Re: World Journal of Virology, Manuscript no: 80792

Dear Editor,

Thank you for the opportunity to submit a revised version of our manuscript "Intestinal barrier dysfunction as a key driver of severe COVID-19" by Tsounis et al. We appreciate the time and efforts that you and the reviewers dedicated to providing valuable comments on our article.

We have now completed the revisions required by the Reviewers and the Editorial Board. All changes are highlighted in the revised manuscript. Point-by-point answers to the comments made by the reviewers are provided below.

The revised manuscript has been seen and approved by all authors.

We hope that our revised manuscript will meet with your approval,

I remain,

Yours sincerely,

Stelios F. Assimakopoulos

REVIEWER #1**Comment**

The review manuscript entitled "Intestinal barrier dysfunction as a key driver of severe COVID-19" by Dr. Tsounis and colleagues provides a detailed overview on the mechanisms of impairment of the gut barrier homeostasis upon SARS-CoV-2 infection. The current state of the art about how intestinal barrier dysfunction might drive severe COVID-19 or induce detrimental complications is also provided. The text is interesting, highly informative, well written and easy to follow. Overall, this topic is quite important and interesting. This review can help to better understand the role of intestinal barrier in counteracting SARS-CoV-2 infection. Figures are highly informative

and well organized. While I recommend the article for publication, I have some minor concerns to be reviewed by authors before such publication:

- Major Although informative, the abstract should be reorganized by reducing its length by 20% for a better readability and by introducing the aim of the review
- A general introductive paragraph describing general notions on intestinal homeostasis and intestinal immune function, before section 4, would be helpful for the reader. Authors can check doi: 10.2183/pjab.92.423 and <https://pubs.rsc.org/en/content/articlelanding/2022/fo/d2fo00911k>
- The topic on SARS-CoV-2 infection and colon cancer should be at least briefly mentioned PMID: 36191449, PMID: 36096812
- Minor 1. Abstract, GI, COVID-19, SARS-CoV-2, as well as other acronyms should be carefully checked and mentioned with their complete name the first time being mentioned.
- 2. Section 2. "The principal route SARS-CoV-2 infection [8]." --->Additional notions on viral proteins and genome are described here <https://www.mdpi.com/2076-2607/10/6/1193> this supporting reference should be included
- 3. Some words throughout the text are highlighted in bold style which should be removed.

Answer

Thank you for your positive remarks.

- The abstract has been reorganized and shortened. The aim of the review has been added.
- An introductive paragraph describing mucosal immune function under homeostatic conditions has been included before Section "The Intestinal Barrier Function in COVID-19."
- The significance of long-term microbiome alterations due to SARS-CoV-2 and their implications in the development of colorectal cancer have been added in the last paragraph of Section "Gut barrier dysfunction: an underappreciated driver of systemic inflammation".
- Acronyms have been carefully checked and mentioned with their complete name the first time they are mentioned, according to the journal's guidelines.
- The genome and proteins of SARS-CoV-2 have been described in greater detail, and the relevant references have also been included.
- The bold-styled words have been corrected.

REVIEWER #2

Comment

The fundamental role of endothelial dysfunction in the systemic manifestations of COVID-19 should be better discussed: -J Clin Med. 2020;9(5):1417; doi: 10.3390/jcm9051417 -Expert Opin Ther Targets. 2020 Jun 27;1-8. doi: 10.1080/14728222.2020.1783243 -Cells. 2020 Jul 9;9(7):E1652. doi: 10.3390/cells9071652 -Biomedicines 2020, 8(11), 462; doi: 10.3390/biomedicines8110462 -Eur Heart J. 2021 May 23;7(3):e2-e3. doi: 10.1093/ehjcvp/pvaa145. -Noncoding RNA. 2021 Feb 2;7(1):9. doi: 10.3390/ncrna7010009 -J Pharmacol Exp Ther. 2022:JPET-AR-2022-001209. doi: 10.1124/jpet.122.001209. -Antioxidants. 2021;10(6):971. doi: 10.3390/antiox10060971. -Pharmacol Res. 2022 Sep;183:106360 -Atherosclerosis. 2021;322:39-50. doi: 10.1016/j.atherosclerosis.2021.02.009. -EClinicalMedicine. 2021 Sep 9;101125. doi: 10.1016/j.eclinm.2021.101125. -Oxid Med Cell Longev. 2021 Aug 21;2021:8671713 -Nutrients. 2021 Nov 5;13(11):3951. doi: 10.3390/nu13113951. -Theranostics. 2021;11(16):8076-8091. -Crit Care. 2021 Aug 25;25(1):306. -Int J Mol Sci. 2022 Sep 6;23(18):10242. -Front Physiol. 2020 Aug 4;11:989. doi:10.3389/fphys.2020.00989 (chronological appraisal of the publications on COVID-19 and endothelial dysfunction).

Answer

Thank you for your positive remarks.

- The fundamental role of endothelium dysfunction that represents a common feature in multiple complications of COVID-19, such as cerebrovascular events, cardiovascular events, renal dysfunction, and neurological complications, has been further described (Ref 138: Sardu C, et al. J Clin Med. 2020; Ref 139: Gambardella J, et al. Eur Heart J Cardiovasc Pharmacother. 2021). The mechanisms through which SARS-CoV-2 inflicts endothelial injury have been further clarified (Ref 141: Gambardella J, et al. J Pharmacol Exp Ther. 2022; Ref 142: Quinaglia T, et al. Atherosclerosis. 2021). The significance of endothelial-derived extracellular vesicles in inducing dysregulation of the blood-brain barrier has been added (Ref 150: Gambardella J, et al. Crit Care 2021; Ref 151: Mone P, et al. Noncoding RNA 2021). The potential of restoring endothelial function to improve patient outcomes has been included (Ref 167: Fiorentino G, et al. EClinicalMedicine 2021; Ref 168: Adebayo A, et al Nutrients 2021).

EDITORIAL OFFICE'S COMMENTS

Comment

(1) Science editor:

The manuscript has been peer-reviewed, and it's ready for the first decision.
Language Quality: Grade C (A great deal of language polishing)
Scientific Quality: Grade C (Good)

(2) Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Virology. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

Answer

Our text has undergone thorough language editing. By using the RCA tool, our work incorporates the most recent cutting-edge research findings.