

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 88866

Title: Alkaline sphingomyelinase deficiency impairs intestinal mucosal barrier integrity and reduces antioxidant capacity in dextran sulfate sodium-induced colitis

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00037490

Position: Peer Reviewer

Academic degree: N/A

Professional title: N/A

Reviewer's Country/Territory: Germany

Author's Country/Territory: China

Manuscript submission date: 2023-10-12

Reviewer chosen by: Yu-Lu Chen

Reviewer accepted review: 2023-11-06 08:06

Reviewer performed review: 2023-11-14 12:06

Review time: 8 Days and 4 Hours

Scientific quality	☐ Grade A: Excellent ☒ Grade B: Very good ☐ Grade C: Good ☐ Grade D: Fair ☐ Grade E: Do not publish
Novelty of this manuscript	☐ Grade A: Excellent ☒ Grade B: Good ☐ Grade C: Fair ☐ Grade D: No novelty
Creativity or innovation of this manuscript	☐ Grade A: Excellent ☒ Grade B: Good ☐ Grade C: Fair ☐ Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	☐ Grade A: Excellent ☒ Grade B: Good ☐ Grade C: Fair ☐ Grade D: No scientific significance
Language quality	☐ Grade A: Priority publishing ☐ Grade B: Minor language polishing ☒ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☐ Accept (General priority) ☐ Minor revision ☒ Major revision ☐ Rejection
Re-review	☒ Yes ☐ No
Peer-reviewer statements	Peer-Review: ☒ Anonymous ☐ Onymous
	Conflicts-of-Interest: ☐ Yes ☒ No

SPECIFIC COMMENTS TO AUTHORS

In this study, the authors investigate the role of the enzyme alkaline sphingomyelinase for the barrier function of the intestinal epithelium during DSS-induced colitis. They confirm that the knock-out of this enzyme worsenes the epithelial barrier by reducing the expression of several components of the tight junctions and thereby worsenes the outcome of the disease. It is speculated that downregulation of the transcription factor Nrf2 is critically involved in these phenomena. However, one key experiment is missing in my eyes to really prove this hypothesis (see my major comments). Major comments: - Statistics is not adequately described: What was the group size (i.e. total number of mice in each group)? In the statistics section, the posthoc test used after the ANOVA (to find out which group is significantly different from which group) must be given. - Fig. 1E: What is the reason to write in the result section that the number of goblet cells was reduced after 6d DSS im the KO group? In the HE staining, you see goblet cells as cells with large cytoplasmic vacuoles and your picture shows MORE of these cells compared to the d0 situation. You should perform PAS staining to clarify this point if possible from your material. - Fig. 3: When using the deltadeltaCt method, the expresion of the

reference gene(s) must be stable under the conditions used (i.e. after the induction of colitis): Was this the case (see The MIQE guidelines: minimum information for publication of quantitative real-time PCR experiments; Clin Chem: 611-622, 2009 for testing)? Otherwise all changes might result from changes in the expression of your "house keeping gene" (GAPDH). - Fig. 7: The idea that changes in the expression of Nrf2 are involved in the described effects is very interesting. However, the experiment depicted in Fig. 7 is not convincing. Maybe Nrf2 activation by t-BHQ would also improve the situation in the WT mice. So you need the key experiment to study the effect of t-BHQ on the course of the colitis in WT animals! Minor comments: - p.4, line 9: I assume you mean the microbiome when you speak about "biological barrier". Perhaps the term "microbial barrier" would be more clear. - Especially in the method section, many abbreviations are used without definition. All abbreviations must be defined at first use throughout the manuscript. - Western blot section: give the source of all antibodies (not only that of ZO-1) - Table 2: Give the gene accession (data base) numbers of all genes for which you give the primers here. Checklist: 1 Title: reflects the results 2 Abstract: concise 3 Key Words: adequate 4 Background: adequate 5 Methods: some explanations are missing, see above 6 Results: One key experiment is missing; see above 7 Discussion: adequate. 8 Illustrations and tables: adequate. 9 Biostatistics: description of posthoc test after ANOVA is missing (see above) 10 Units: okay 11 References: okay 12 Quality of manuscript organization and presentation: in general well structured. 13 Research methods and reporting: okay 14 Ethics statements: okay

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

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Position: Peer Reviewer

Academic degree: N/A

Professional title: N/A

Reviewer's Country/Territory: Germany

Author's Country/Territory: China

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Reviewer chosen by: Jing-Jie Wang

Reviewer accepted review: 2024-01-06 09:09

Reviewer performed review: 2024-01-10 11:11

Review time: 4 Days and 2 Hours

Scientific quality	☐ Grade A: Excellent ☐ Grade B: Very good ☒ Grade C: Good ☐ Grade D: Fair ☐ Grade E: Do not publish
Language quality	☐ Grade A: Priority publishing ☒ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☒ Accept (General priority) ☐ Minor revision ☐ Major revision ☐ Rejection
Peer-reviewer	Peer-Review: ☒ Anonymous ☐ Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Adequate revision