Author's response to reviews

Title: Mitochondria-targeted antioxidant MitoQ ameliorates experimental mouse colitis by suppressing NLRP3 inflammasome-mediated inflammatory cytokines

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Author's response to reviews: see over
Dear Dr. Sabina Alam

RE: Manuscript MS: 3967196349611999
Manuscript title: Mitochondria-targeted antioxidant MitoQ ameliorates experimental mouse colitis by suppressing NLRP3 inflammasome-mediated inflammatory cytokines.

We would like to thank you for giving us the opportunity to revise our manuscript. As the reviewers suggested in your letter on May 10th, we have revised the manuscript again. We hope that the present manuscript will be deemed acceptable for publication in the BMC-Medicine.

The following provides our point-by-point responses to the reviewer’s comments. In addition, the figure 7 was made exclusively for this study to support our hypothesis. We believe the statements presented in response to the reviewer’s comments have allowed us to further improve our manuscript. We would appreciate your reviewing our revised manuscript and look forward to hearing from you soon.
Reviewer 1

Reviewer: Holger K Eltzschig

Reviewer's report:

The present studies show that ROS originated form mitochondria play a causative role in the pathogenesis of IBD. ROS levels, oxidative injury and inflammatory cytokines IL-1beta and IL-18 were increased in colon tissue of DSS-induced colitis mice and significantly decreased by treating with MitoQ. Also, excessive activation of NLRP3 inflammasome which is responsible for those cytokines was suppressed by MitoQ. Based on these findings the authors conclude that mtROS play a critical role in the pathogenesis of IBD and MitoQ is a possible therapeutic molecule for the
treatment of IBD. These are novel and important findings. The conclusions are well supported by the data presented.

Major comments:

1. The authors should expand their discussion on the interdependent role of hypoxia and inflammation (see for example Eltzschig et al. Hypoxia and Inflammation; NEJM 2011 and Eltzschig et al. Purinergic signaling during inflammation; NEJM 2012). How does the hypoxic environment of the inflamed mucosa impact their findings?
Response: In accordance with reviewer’s suggestion, the discussion in the manuscript is expanded with hypoxia, inflammation and ROS. (Please read the line 20-31 in the 2nd paragraph of the “Discussion”).

2. What role do regulatory T cells play in this context (see for example Clambey et al. Hypoxia-inducible factor-1 alpha-dependent induction of FoxP3 drives regulatory T-cell abundance and function during inflammatory hypoxia of the mucosa; PNAS 2012)?
Response: Possible role of regulatory T cells in our context is described in the manuscript. (Please read the line 4-8 in the 2nd paragraph of the “Background” and line 28 in the 2nd paragraph of the “Discussion”).

Reviewer 2
Reviewer: Atsushi Mizoguchi

Reviewer’s report:
This manuscript proposes the potential therapeutic effect of MltoQ (an orally available mitochondria-targeted derivative of the antioxidant ubiquinone) on acute colonic injury induced by oral administration of dextran sulfate sodium (DSS). Overall, this is a well written manuscript that contains attractive and translational information. However, there is a terminological, but important, issue to be corrected for avoiding mislead the readers.

1. Minor Essential revision: The authors emphasize DSS colitis as a model of inflammatory bowel disease (IBD). Although DSS colitis is useful to study the mechanism of acute intestinal damage and following wound healing process, it is still under very controversy
whether this injury model can be used as a model of IBD. In addition, the authors used an unusual protocol for DSS administration, which should cause continuous epithelial damages by the chemical. Therefore, the authors need to change the term “IBD’ to “acute colonic damage or injury”. If the authors eager to keep it, additional studies to test the therapeutic effect of MitoQ on another well accepted mouse IBD model (e.g. IL-10 knockout mice) would be necessary.

Response: According to reviewer’s suggestion, we modified the statement. But, in some conditions we used the term “acute phases of IBD” in reference to other publications (J Immunol. 2012, 188(12):6309-18; Am J Physiol Gastrointest Liver Physiol 2010, 298(6):G878-83). (Please read the last line in conclusion of the “Abstract”; the last paragraph of the “Background”, the last line in the “Result”, the last line in the 3rd paragraph of the “Discussion”, line 6-8 in the conclusion of the “Discussion”).