

## ANSWERING REVIEWERS

**Title:** Inflammatory and oxidative stress in rotavirus infection

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The manuscript has been improved according to the suggestions of reviewers:

### **Reviewer #1**

The present manuscript tries to review the role of oxidative stress and inflammation responses and signaling in rotavirus infection and pathogenesis with an emphasis on cellular proteins having oxidoreductase, thiol isomerization and chaperone activities in connection to rotavirus entry into the host cell and finally discuss potential therapeutic approaches targeting them. Major comment: Taken together, manuscript is well written, well organized and compromise the major and available knowledge in the domain. However for a review article with such great insights and extents, the manuscript suffers from lack of: 1. "Specially designed Figures and tables" to summarize and collect the presented knowledge and data in the manuscript. 2. Concluding remarks at the end of each section to figure out the prospect of future research in the specified domain presented in each section. 3. Improving the text and presentation of data to better relate the inter- and intra-presented knowledge in sections to give a general picture on the main subject of the manuscript. Minor comments: I would suggest to include some related studies in case of animal rotavirus infections and role of inflammatory and oxidative stress and potential role of interacting bacterial infections with rotavirus infection. Some examples are in the following: Alterations in oxidant/antioxidant balance, high-mobility group box 1 protein and acute phase response in cross-bred suckling piglets suffering from rotaviral enteritis. Kumar De U, Mukherjee R, Nandi S, Patel BH, Dimri U, Ravishankar C, Verma AK. Trop Anim Health Prod. 2014 Oct;46(7):1127-33. doi: 10.1007/s11250-014-0616-3. Epub 2014 May 22 Malnutrition modifies pig small intestinal inflammatory responses to rotavirus. Zijlstra RT, McCracken BA, Odle J, Donovan SM, Gelberg HB, Petschow BW, Zuckermann FA, Gaskins HR. J Nutr. 1999 Apr;129(4):838-43 Klebsiella pneumoniae bacteraemia complicating rotavirus gastroenteritis in two infants with glucocorticoid deficiency. Longmore DK, Batch JA, McMahon SK, Conwell LS. J Pediatr Endocrinol Metab. 2010 Mar;23(3):293-5.

### **Response to the reviewer**

#### **Major comments**

1. We agree with the reviewer's comment. We have now designed four Figures and a Table to illustrate the rotavirus-induced inflammatory and stress oxidative pathways as well as the entry mechanisms involving chaperone and oxido-reduction activities of some cell surface receptor molecules.
2. According to the reviewer's suggestion, we have now improved the manuscript by adding some concluding remarks at the end of each section to highlight some prospects of research in the respective fields.

3. An attempt has now been made to improve the presentation of data within the sections and between sections to ensure a general picture on the main subject throughout the manuscript.

#### **Minor comments**

In line with the reviewer's recommendation, we have now included a brief description related to animal rotavirus infections and role of inflammatory and oxidative stress and also to potential role of interacting bacterial infections with rotavirus infection.

#### **Reviewer #2**

This review is excellent. Just a few grammar/spelling errors but overall very well written.

#### **Response to the reviewer**

The text has now been carefully revised and the grammar/spelling errors corrected.

#### **Reviewer #3**

This is well-written review article on "Inflammatory and oxidative stress in rotavirus infection". The authors have made a comprehensive analysis of the role of inflammatory and oxidative stress in rotavirus infection. Thus, this review article is important for the field. However, the review will be much improved if the authors will consider the following: 1. The abstract indicate that authors focused mainly on the role of inflammatory and oxidative stress in rotavirus infection. However, this review covered the multiple aspects of rotavirus infection, including the role of innate immune response in rotavirus infection. Moreover, the innate immune section has broad discussion with multiple viruses, which are irrelevant to rotavirus infection. It will be good, if authors will focus on discussion of important aspects of inflammatory and oxidative stress in rotavirus infection. The role of innate immune response including TLRs in rotavirus infection could be another review. 2. Authors, often refers multiple viruses through the review, which are not relevant to rotavirus infection. 3. The authors present a large amount of published information showing multiple proteins/enzymes and signaling pathways of inflammatory and oxidative stress, which may play critical role in rotavirus infection. This should be presented as a table(s) or schematic diagrams; otherwise, it will be hard for the readers. 4. The authors need to create models (cartoons) showing the potential molecular mechanism of inflammatory and oxidative stress in modulation of rotavirus infection. Such cartoons could be created in each section and one summary model could be generated for "concluding remarks" section, which may show the role of inflammatory and oxidative stress in molecular pathogenesis of rotavirus infection.

#### **Response to the reviewer**

1. According to the reviewer's recommendation, the section about innate immune response has now been enlarged with aspects more specifically related to rotavirus infection. We agree with the reviewer's suggestion that the role of innate immune response in rotavirus infection could be another review. However, the omission of a brief analysis related with the innate immune response in virus infections would constitute a critical gap in the understanding of the role of inflammasomes during recognition of viral stimuli. The brief analysis of innate immune

response can also give context to the role that NF- $\kappa$ B activation plays in virus infection and oxidative stress responses.

2. We agree with the reviewer's comment that viruses other than rotaviruses are referred to through the review. The reason for that is that mentioning some specific findings about other viruses lends support to hypotheses and mechanisms involving rotavirus infection.

3. We agree with the reviewer's comment. We have now presented some cell surface molecules and their functions in a Table. A schematic representation of a summary model about the mechanisms explaining rotavirus entry into the target cell has now been included in the manuscript.

4. A schematic model representing the molecular mechanism of inflammatory and oxidative stress in the modulation of rotavirus infection has now been generated and illustrated in two Figures.