

Author's reply to reviewer's comments

Manuscript no. 20785, entitled Life and death at the mucosal-luminal interface: new perspectives on human intestinal ischemia-reperfusion

***Reviewed by 03342744***

The authors wrote a review in a field with significant importance. In general, it is a well-done work. However, I'm afraid the main topic of the review is not novel. The authors reviewed too much knowledge in old publications, with only 19 publications published after 2010. If the authors summarize the general knowledge in a brief way, and point out the possible ways towards better detection, prevention and therapy, that will be more appreciated. Minor mistakes: the information of reference 23, 28 and 71 should be added.

**Author's response: We have addressed the concerns of the reviewer by adding a section to the current manuscript, entitled 'Translation to clinical practice'. We apologize for the missing information in reference 23, 28 and 71. This information has been added.**

***Reviewed by 03117433***

This review by Grootjans et al. is a well composed summary of current knowledge of intestinal I/R injury covering important aspects of this pathophysiology with a focus on the disruption and re-establishment of the intestinal barrier. As the authors rightfully point out, intestinal I/R injury is a clinically relevant entity, albeit it is very difficult to study in patients due to a lack of sensitive and specific markers or clinical signs. Consequently, most of our knowledge on this condition stems from animal models but multiple problems with current experimental approaches persist (see Gonzalez et al. Am J Physiol Gastrointest Liver Physiol 2015). Therefore the establishment of a human I/R injury model is a major advance towards studying real-life events and their

relevance. The review is well structured, includes important current findings and provides the novel aspects of new research approaches in format that is interesting and easily readable to the interested public. I have only minor comments: -given the novelty of the human I/R model, I miss a diagram that graphs the experimental approach.

**Author's response: A diagram of the experimental approach have been published elsewhere (Derikx et al. J. Surg Res 2009). This information was added to the current manuscript.**

The great importance of this experimental approach is of course the translation of our current, mostly mouse-based knowledge of I/R into what is really going on in patients. The authors very nicely present the findings in the human model, but I would encourage a more distinct juxtaposition of similarities and differences between mouse and men that this work has uncovered and what the distinct advantages/disadvantages of animal models vs. this human model (e.g. are interventional studies possible?)

**Author's response: where appropriate, we have added similarities in pathophysiology between human and mouse studies to the current manuscript. However, we feel that the scope of this manuscript is mainly to describe and summarize the pathophysiology of human intestinal IR, rather than to compare human versus animal studies.**

Also I would encourage a more pointed outlook section specifying what pressing questions this model will serve to answer as the next steps? In what directions can it be developed further?

**Author's response: a section entitled 'translation to clinical practice' has been added to the manuscript.**