Cover Letter September 28th, 2018

Dear Dr. Lian-Sheng Ma,

Editor-in-Chief of *World Journal of Gastroenterology*,

On behalf of my group, I have the pleasure to present this revised version of Manuscript #02998290, "Damage-associated molecular patterns in inflammatory bowel disease: from biomarkers to therapeutic targets", for your consideration.

We thank the four reviewers for finding the results of our study interesting and for reading in detail our review about DAMPs in IBD. The changes and amendments made to the manuscript continue to support and preserve the general idea of the article. We agree that our text is even more consistent after the changes and new references, greatly contributing to improving the manuscript.

In addition, we hereby certify that all authors concur with the submission of this work and that none of the data presented have been previously reported or are under consideration for publication elsewhere.

Thank you for your invitation and consideration,

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Manuscript #02998290: "Damage-associated molecular patterns in inflammatory bowel disease: from biomarkers to therapeutic targets"

Reply to the reviewers

Reviewers' Comments:

Peer-review report

Reviewer #1: This is a comprehensive review of DAMP biology and relevance to IBD.

Specific Comments

1. The Figures are mentioned in the text of the MS, but there are no legends to go with the Figures in proximity

We understand this reviewer's comment, and we have placed the legends immediately beneath the figures.

2. The S100 family comprises many more proteins than the 5 listed. This should be corrected.

We agree with this reviewer's comment, and we have corrected the text regarding the S100 family.

3. Interleukins should be abbreviated as IL and not as Il 4.

We apologize for the mistake. We have corrected any incorrect abbreviations.

We thank Reviewer#1 for the attentive reading of our manuscript and for his/her support of our work.

Reviewer #2: Dr. Nanini and Dr. de Souza, et al. reviewed 'Damage-associated molecular patterns in inflammatory bowel disease: from biomarkers to therapeutic targets'. The article is well-presented. The reviewer has some comments.

Comments

1. In page 6 line 9, the authors described 'damage-associated molecular patterns (DAMPs), please use just 'DAMPs'. Because the authors already used 'Damage-associated molecular patterns (DAMPs)' in page 5 line 16.

The sentence has been corrected, removing the description.

2. In page 7 line 9, the authors used a term 'ATP', this abbreviation was listed for the first time. Please list it without an abbreviation.

We apologize for the mistake. An appropriate description has been added to the text.

3. In References, please correct and list Journal names following contribution rule in WJG.

We are surprised about this mistake, and we apologize. In EndNote X7, we updated the references style regarding WJG according to the program settings.

We thank Reviewer#2 for the attentive reading of our manuscript and for his/her support of our work.

Reviewer #3: It is interesting manuscript but need to be more specific.

The biomarkers with clinical utility should be clearly presented and separated according the disease phenotype CD or UC. The data should be clearly regarding the two IBD entities.

We understand the reviewer's point of view, and we attempted to identify more clearly data concerning disease phenotypes. Additional information on specific disease phenotypes was added to the text, and data are highlighted in a new Table (Table 1). Additional references have also been included.

The animal studies should be separated from clinical data.

We understand this reviewer's point of view, and we generated a Table (Table 1) in which we show, in separate columns, human and experimental studies with their own specificities.

We thank Reviewer#3 for the attentive reading of our manuscript and for his/her support of our work. These suggestions significantly contributed to improving our manuscript.

Reviewer #4: The authors provide an interesting overview of damage-associated molecular patterns (DAMP) and of pattern recognition receptors (PRR). The review is timely and addresses an innovative field of active research. In general, this is a clear and easy to read review.

The main limitation is that upon reading the title and considering the clinical readership of the Journal, I would like to see more focus on the clinical aspects.

1) I would expect more specific focus on which biomarkers are actually (at least potentially) useful for each disease (CD vs UC) and which targets can realistically be exploited clinically in the next few years (experts' opinion, which would be an added value for this manuscript)

We understand the reviewer's point of view and concerns, and we attempted to increase our focus on the specificities and potential of DAMPs as targets for therapy. However, we need to recognize the current limitations of defining functions, phenotypic specificities, and therapeutic use, as most data indicate considerable overlapping effects and suggest that DAMPs alone and the network of interactions in which they participate need to be further elucidated.

2) Considering item 1 above, in my opinion the core tips and the abstract are too generic in the present form. They should provide more insight into what major issues must be faced by future research in the field.

We again understand the reviewer's point of view and concerns, and we attempted to improve the text regarding the core tips and the abstract with more specific data.

3) The authors consider IBD in general, but some more effort should be done to address these questions: a) are there differences in DAMPs in CD and UC? b) which of the described pathways are already being exploited by pharmacological research? (for instance purinoceptors are only briefly mentioned, whereas a long list of studies is available and should be critically addressed, at least briefly);

We agree, and we accepted the challenge of preparing a summary showing differences in DAMPs between CD and UC and also comparing human with animal studies (new Table 1). Additional references have been included. Because of space limitations imposed by the

editorial office, we concentrated on studies with more consistent associations with IBD and that were less speculative.

4) Data from animal models should be clearly separated from clinical data (tables in this case could be very helpful to summarise data). For each animal model, its face validity, construct validity and predictive validity should be at least briefly addressed.

We agree with the reviewer's comment, and we added a Table to summarise the most consistent studies (new Table 1).

Minor points. - It is stated that the first two authors contributed equally to this work, but in the submission letter it is indicated that "Please note that the designation of co-first authors and co-corresponding authors is not permitted".

We have corrected the misunderstanding regarding the co-first authors.

Please check. - The English style can still be improved (especially some sentences can be shortened and be more focused).

The language style has been revised for appropriateness, as suggested.

We thank Reviewer#4 for the attentive reading of our manuscript and for his/her support of our work. These suggestions significantly contributed to improving our manuscript.