Yuan Qi
Scientific Editor
World Journal of Gastroenterology

October 28, 2016

Dear Dr Qi,

Re: Manuscript reference No. 30250

Please find attached a revised version of our manuscript “Visceral hypersensitivity in gastrointestinal inflammation: the role of proteases”, which we would like to resubmit for publication as a Review in World Journal of Gastroenterology.

Your comments and those of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. In the following pages our responses to each of the comments of the reviewers as well as your own suggestions can be found.

Revisions in the text are shown using yellow highlights for additions, and strikethrough fonts for deletions. In accordance with the suggestion of reviewer #2, we inserted a paragraph on the subject of the location of the different PARs in various cell types in the gastrointestinal tract.
We hope we addressed the comments and suggestions satisfactorily and that the revisions in the manuscript and our accompanying responses are sufficient to make our manuscript suitable for publication in World Journal of Gastroenterology.

We look forward to hearing from you.

Yours sincerely,

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Responses to the comments of Reviewer #1 – No. 3644009

1. Page 7, serine protease inhibitors are summarized in Table 1: This table contains Gliptins as DPP-IV inhibitor. Gliptin is an inhibitor of DPPIV which is a serine dependent peptidase belonging to family S9 (Prolyl oligopeptidase). Its serine active site is sensitive to DFP. DPPIV is a member of a novel family of non-classical serine proteases, but not a conventional serine-protease. It inactivates incretins: glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (in) or glucose-dependent insulinotropic peptide (GIP). Inhibition of DPP-4 leads to a significant increase in the concentration of GLP-1 and GIP that cause an increase in insulin secretion and a reduction in glucagon secretion property to improve the balance in sugar in diabetics. The gliptins are thus part of the molecules playing on increasing the incretin rate.

Response: Indeed, DPP-IV is a non-conventional serine peptidase belonging to the family of the S9 – prolyl oligopeptidase. This information has been added to table 1 as a footnote..

2. Page 7, Figure 3 was mentioned in line 8. This figure illustrates PAR activation, it should be mentioned later at the same page (line 16)

Response: We now refer to figure 3 later on the same page, in the paragraph where the PAR activation process is explained (as highlighted on page 7).

3. Figure 2: Title to be corrected, the authors can add illustrative examples of serine proteases: plasmin and kallikrein

Response: The title is corrected and plasmin and kallikrein are now added as examples of serine proteases in the table.

4. table 3: Aprotinin is not a specific inhibitor for Trypsin, it inhibits many enzymes including plasmin, kallikrein and FXIIa.

Response: The referee is correct, we added the target enzymes of aprotinin to table 3.

Responses to the comments of Reviewer #2 – No. 3529970

1. The review is very well written and provide a detailed information about role proteases through activation of PAR receptors in visceral hypersensitivity. Moreover the review describe also possible application of protease inhibitors in treatment of the disease. From my point of view only one small thing is missing in the review: information about the prevalence of each PAR receptors in cells forming human gastrointestinal tract, especially in epithelial cells. It is important, because PAR receptors are not equally distributed among human cells. Such paragraph will improve the scientific value, which now is high, of the review.

Response: We certainly agree with this comment that this additional paragraph improves the scientific value of the review. Therefore, we added a paragraph concerning the prevalence of the different PARs on various cell types in the gastrointestinal tract. This paragraph can be found on p.6.

2. abstract: "catalyzing the cleavage of peptide bonds": instead of cleavage it should be hydrolysis (at least for the first time in the text, then it could be cleavage)

Response: We have changed 'cleavage' into 'hydrolysis' in the abstract as well as in the core tips.

3. abstract: "can be classified into several clans": according to MEROPS database protease clans contains proteases sharing common evolutionary origin. One clan could contain both serine and cysteine proteases. As a result this fragment in the text is not correct. Suggestion: classified based on chemical mechanism of catalysis into several classes.

Response: We followed the suggestion of the referee and altered this sentence in the abstract.

4. page 5: in the paragraph starting from: "At the peripheral level, inflammatory cells, e.g. mast cells, T-cells..." there is no references, but they should. Please add appropriate references.

*Response: Appropriate references have been added: De Schepper HU, De Man JG, Moreels TG, Pelckmans PA, De Winter BY. Review article: gastrointestinal sensory and motor disturbances in inflammatory bowel disease - clinical relevance and pathophysiological mechanisms. Aliment Pharmacol Ther 2008; **27**: 621-37 [PMID: 18221407 DOI: 10.1111/j.1365-2036.2008.03624.x].*

5. page 6: "releasing a single amino acid or a dipeptide, respectively": it is not correct, because exopeptidase could release from N-terminus an amino acid, a dipeptide, a tripeptide and from C-terminus: an amino acid and dipeptide. Please change it.

Response: This inaccuracy has been corrected in the text according to the referees suggestion.

6. Figure 1: please mark all peptide bonds which could be cleaved by exopeptidase at both protein termini.

Response: All peptide bonds that could possibly be cleaved by exopeptidases are now marked in figure 1.

7. Figure 2: in heading please remove: "This scheme represents".

Response: We removed this part of the heading as suggested by both referees.

Responses to the comments of the Editor

1. Please add the keywords "inflammatory bowel diseases" in the title.

Response: The keywords inflammatory bowel diseases and irritable bowel syndrome have been added to the title. However this results in a title of 14 words, so we hope that is all right for the editor then.

2. Conflict-of-interest statement: This file must be signed by the corresponding author and provided in a PDF format, and the statement must also be mentioned as a footnote in the manuscript text.

Response: The conflict-of-interest statement will be provided in a PDF format. The statement has also been mentioned as a footnote.

3. Figure 1, 2 & 3: Please provide the decomposable figure of Figures, whose parts are movable and can be edited. So please put the original picture as word or ppt or excel format so that I can edit them easily.

Response: The original, decomposable figures are provided in Powerpoint format as requested.