

Dear Editor,

I would like to thank reviewers for their constructive criticism of an earlier version of our manuscript entitled "The Role of Regenerating Islet-Derived Proteins in Inflammatory Bowel Disease". Their comments have provided critical guidance for us to modify our manuscript. In the attached point to point responses, please find the detailed descriptions of the modifications highlighted in our current version. We hope that we have fully addressed reviewers' concerns and that this revision is more readable and interesting to a broad range of your readers. We thank you again for your thoughtful consideration for publication of our manuscript as a review in World Journal of Gastroenterology.

Sincerely,

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Point to Point Responses

Reviewer 04091933 (Specific Comments to Authors):

The manuscript is highly relevant, since Reg proteins seem to assume important roles as pro-proliferative, anti-apoptotic and bactericidal agents may serve as biomarkers and therapeutic targets. The manuscript can certainly be recommended for publication, but after a minor revision.

Response: We are grateful for Reviewer 04091933's positive and insightful comments. These comments provided critical guidance for the revision of the manuscript.

1) I consider it appropriate to use only one of the terms REG protein or Reg protein, but not a double term REG/Reg protein (or REG/Reg gene).

Response: We understand the importance of simplicity. However, despite the similarities, the functions and sequences of mouse Reg proteins and human REG proteins are not identical. As per PubMed's recommendations, we use REG and Reg to represent human and mouse proteins respectively. We apologize for the inconvenience.

2) The authors provided well-constructed and well-annotated tables and figures. However, the Table 2 requires removing italics from the names of Classes, Orders, Families, and using italics only for Genera. For Clostridium, it must be clarified that XI and XIVa are clusters. In Table 1, in my opinion, an important study by Planell et al., 2013 (REG1A, REG4 expression in UC patients) is missing. This study should also be discussed.

Response: We appreciate your constructive criticism which helps to improve our manuscript. We have modified Table 2 according to the scientific nomenclature recommended by "Centers for Disease Control and Prevention (CDC)" that "Italics are used for bacterial and viral taxa at the level of family and below" (<https://wwwnc.cdc.gov/eid/page/scientific-nomenclature>). We have therefore used the italics for bacterial taxa at the level of family and genera. We have also indicated that XI and XIVa are Clusters in the table. Additionally, as suggested, we have added the important study by Planell et al., 2013 (Ref#49) in Table 1. We have also added multiple sentences highlighted on page 8, 9 and 10 to describe and discuss this study. As a result, two more references (Ref#74,75) have been added, and TGF-beta1/GATA4 pathway has been added in Figure 1 in the current version.

3) The authors reasonably cite the latest, relevant and comprehensive references. Self-citation was appropriate (2 references only, 1.8%). I also recommend including the reference and discussing new important study on Reg3B by Shindo et al., 2020 (PMID: 32072024).

Response: Thank you for the comment and suggestion. We have added the new important study by Shindo et al., 2020 (Ref#22), and described and discussed it on page 5 and 13 respectively (highlighted).

Reviewer 03733644 (Specific Comments to Authors):

This is a very interesting review enriched our knowledge on the mechanism of IBD. However, there some points should be pay attention.

Response: We are grateful for Reviewer 03733644's positive and constructive comments. These comments provided critical guidance for the revision of the manuscript.

1. *"Regenerating Islet-Derived (Reg) Proteins" replace of "Regenerating (REG/Reg) proteins".*

Response: We have replaced "Regenerating (REG/Reg) proteins" with "Regenerating islet-derived (REG/Reg) proteins" in the manuscript (Page 1, 3 and 4).

2. *"Interestingly, despite Reg4's trophic effects on intestinal epithelium, Reg4 deficient mice had a less severe form of DSS-induced colitis associated with altered compositions of the intestinal microbiota, suggesting a dominant role of the altered bacteria population in colitis". As we know, DSS-induced colitis was the IBD animal model. So, I suggest this sentence add in the "Increased expressions of REG proteins in IBD patients" section.*

Response: As suggested, we have removed this sentence in the section of "REG/Reg proteins and their beneficial effects on intestinal homeostasis". Since we have a similar description (Notable among these are that mice with REG3 α overexpression and mice with Reg4 deficiency were resistant to DSS-induced colitis, suggesting the importance of REG/Reg-regulated intestinal microbiota in IBD pathogenesis) highlighted in the section of "REG proteins are potentially protective in IBD" on page 12, we did not add an additional description in the section of "Increased expressions of REG proteins in IBD patients" in order to avoid redundancy.

3. *"Although the complex pathogenesis triggered by the interplay of genetic, immunologic, microbotic, and environmental factors in IBD has not been fully worked out, defective bacterial clearance, aberrant immune responses, and impaired epithelial barrier have been recognized as key defects that drive IBD progression". This sentence was unnecessary and I suggest to remove it.*

Response: We agree. We have removed this long sentence on page 10 and replaced it with "Studies have supported that IBD progression is driven by defective bacterial clearance, aberrant immune responses, and impaired epithelial barrier" (highlighted).

4. *"Non-invasive imaging such as ultrasound, and CT and MR enterography.....FMT, et al. This section was too redundant and I suggest to simplify it.*

Response: We agree. These two paragraphs have been simplified and highlighted on page 13 and 14.

Reviewer 03657249 (Specific Comments to Authors):

This is a review concerning discussion of REG proteins. I said yes to review this article due to its focus on proteins to regenerate damaged tissue in IBD. It is an article focusing on chemical processes of various REG proteins. CD and UC are also characterized by different cytokine responses to REG proteins. There is a focus on the sub-level - the parts in the organism and the interesting thing is how this is included in homeostatic processes. This is shown in figure 2 where the REG proteins are potentially protective in IBD. This model shows an interesting wholeness perspective and illustrate coherence. They have an anti inflammatory effect with tissue repair and the bacteria that maybe is causing infection. This shows the importance of the microbiome ability to be able to repair tissue. Further, the article goes on to show how REG proteins can become a potential diagnostics test, from physical examinations to search for bio markers with the possibility to potentially find protective bacteria.

Response: We are grateful for Reviewer 03657249's positive and helpful comments, which suggest an important direction for the future studies of REG proteins in IBD.

I would like to ask a question, if proteins from food have an effect on the recovery or tissue repair of the intestinal epithelium and the composition of the food we eat also have an impact on the composition of the gut microbiome as a whole organism? May this also have an effect on increased or decreased levels of REG proteins? The article should be rewritten for the readers of the journal to reach a broader audience. I recommend that the content of the article focus more of the broader pictures in repairing IBD with the proteins as cell builders.

Response: We understand that a review paper should be interesting to a broad range of readers, and we appreciate the importance of understanding the effects of diet on IBD progression. We have modified a significant portion of this manuscript (page 8-10, 13 and 14, Table 1 and 2, and Figure 1) in order to make it more readable and interesting. Particularly, a paragraph (highlighted second paragraph on page 10) has been added to emphasize that factors such as diet possibly play a role in the regulation of intestinal REG expressions in IBD as well. As a result, a new reference (Ref#78) has been added. However, due to the absence of studies of relationships between REG expressions and diet in IBD patients, we regret that we are unable to include any further discussions on this topic currently.