



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 54141

**Title:** The role of regenerating islet-derived proteins in inflammatory bowel disease

**Reviewer's code:** 03657249

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** Norway

**Author's Country/Territory:** United States

**Manuscript submission date:** 2020-01-21

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2020-01-23 13:52

**Reviewer performed review:** 2020-02-04 20:41

**Review time:** 12 Days and 6 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**



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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 bacterias. 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.



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 54141

**Title:** The role of regenerating islet-derived proteins in inflammatory bowel disease

**Reviewer’s code:** 03733644

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Attending Doctor

**Reviewer’s Country/Territory:** China

**Author’s Country/Territory:** United States

**Manuscript submission date:** 2020-01-21

**Reviewer chosen by:** Ruo-Yu Ma

**Reviewer accepted review:** 2020-02-21 23:55

**Reviewer performed review:** 2020-02-24 06:47

**Review time:** 2 Days and 6 Hours

<b>Scientific quality</b>	<input checked="" type="checkbox"/> Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
<b>Language quality</b>	[ ] Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
<b>Conclusion</b>	[ ] Accept (High priority) [ ] Accept (General priority) <input checked="" type="checkbox"/> Minor revision [ ] Major revision [ ] Rejection
<b>Re-review</b>	[ ] Yes [ ] No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes <input checked="" type="checkbox"/> No

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This is a very interesting review enriched our knowledge on the mechanism of IBD. However, there some points should be pay attention. 1. "Regenerating Islet-Derived (Reg) Proteins" replace of "Regenerating (REG/Reg) proteins" 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. 3. " Although the complex pathogenesis triggered by the interplay of genetic, immunologic, microbiotic, 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. " 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.



### PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

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**Title:** The role of regenerating islet-derived proteins in inflammatory bowel disease

**Reviewer's code:** 04091933

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Associate Professor, Senior Researcher

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**Author's Country/Territory:** United States

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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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. 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). 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. 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 Reg3 $\beta$  by Shindo et al., 2020 (PMID: 32072024).