

November 12th, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 18982-review.docx).

Title: A role of regulatory T cell in the pathogenesis of inflammatory bowel disease

Author: Akiko Yamada, Rieko Arakaki, Masako Saito, Takaaki Tsunematsu, Yasusei Kudo, Naozumi Ishimaru

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 18982

The manuscript has been improved according to the suggestions of reviewers:

To Reviewer #1 (**Reviewer's code:** 00013033)

Q1. the paper is too long, please shorten and better focus

As suggested by Reviewer, we deleted the last paragraph of the section of “therapeutic Treg cell-based strategies for IBD” to shorten the paper in the revised manuscript.

Q2. authors should add a Figure explaining the role of Treg-s in the pathogenesis in CD/UC and early vs late disease.

As suggested by Reviewer, we added a figure showing the role of Treg cells in the pathogenesis of IBD in the revised manuscript.

To Reviewer #2 (**Reviewer's code:** 02569700)

Q1. the whole manuscript urgently needs orthographic corrections and a rechecking of

wording.

We re-checked wording throughout the revised manuscript.

Q2. Especially, abbreviations need to be rechecked (sometimes it is DDS instead of DSS), species names are sometimes wrong (eg Helicobactor instead of Helicobacter).

We rechecked abbreviations in the revised manuscript.

Q3. A list of abbreviations is strongly recommended.

As pointed out by the Reviewer, we added a list of abbreviations in the revised manuscript.

Q4. Here are some examples of mistakes: “In the intestinal epithelium, four cell types columnar cells, goblet cells, endocrine cells, and leukocytes to rest on a continuous basement lamina”..... please change wording

We corrected the sentence in the revised manuscript.

Q5. “In addition, the immune cells in the lamina propria, the leukocytes also involve various immune cells, such as the unique immune cell types that exist in gut- or mucosa-associated lymphoid tissues such as Peyer’s pacths, mesenteric lymph nodes, and isolated lymphoid follicles”... please change wording Peyer’s patches instead of Peyer’s pacths

We corrected the word in the revised manuscript.

Q6. “As spontaneous models of IBD, several animal models mice and rats are known to use to understand the pathogenesis of IBD or investigate new therapeutic strategy for IBD[9,38].”..... please change wording

We changed it in the revised manuscript.

Q7. C. rodentium - please write out the generic name (Citrobacter?)

C. rodentium is Citrovacter rodentium. We spelled out it in the revised manuscript.

Q8. “Overexpression of TNF and STAT4 gene in mice results in the development of IBD-like lesions”....you mean TNF alpha?

TNF means TNF- α . We added “ α ” in the revised manuscript.

Q9. It should be C3H/HeJBir and not C3HHeJBir mice

C3HHeJBir was changed to C3H/HeJBir in the revised manuscript.

Q10. C. Jejuni...please write out C. It should be Campylobacter jejuni ??

We spelled out it in the revised manuscript.

Q11. “Similar to activated conventional T cells, this Treg cell population exhibits phenotypesand Treg cells with this phenotypic profile are thought to have encountered antigens”... please reword

We modified it in the revised manuscript.

Q12. it should be ROR γ (t) instead of Roryt

ROR γ (t) was changed to Roryt in the revised manuscript.

Q13. F. prausnitzii...F. should be written out (or use abbreviation list)

We spelled out it in the revised manuscript.

Q14. CD4CD8 $\alpha\alpha$it is better to write CD4+CD8+ $\alpha\alpha$

CD4CD8 $\alpha\alpha$ was changed to CD4⁺CD8⁺ $\alpha\alpha$ in the revised manuscript.

Q15. “...the human small intestine in a CB-17 severe combined immune deficiency (SCID) xenotransplant model...” There should be a dot between C and B. They are called C.B-17 SCID mice

CB-17 was changed to C.B-17 in the revised manuscript.

Q16. What is 7-AAG??? Please explain

The sentence including 17-AAG was deleted in the revised manuscript.

Q17. “Pretreatment with a prolactin inhibitor psychology stress-induced dysfunction of Treg cells to facilitate intestinal inflammation[137].”...please reword

The sentence was deleted in the revised manuscript.

Q18. Table 1 DSS instead of DDS

DDS was changed to DSS in the revised manuscript.

Q19. Helicobacter instead of Helicobactor

Helicobactor changed to Helicobacter.

Q20. What is TG in STAT4TG...transgenic? please add abbreviations!

TG was added to abbreviation list.

To Reviewer #3 (**Reviewer's code:** 03415944)

Thank you so much for valuable comments.

Q1. In my opinion the manuscript needs to be revised carefully once again, because some minor linguistic errors.

As suggested by Reviewer, the revised manuscript was carefully checked.

Q2. In my opinion the scheme showing the summary of Treg cells possible involvement in pathogenesis of IBD will be a big advantage of manuscript.

As suggested by Reviewer, Figure showing the pathogenesis was added to revised manuscript.

Thank you so much for processing our manuscript.

Sincerely yours,



Naozumi Ishimaru, D.D.S., Ph.D.

Professor

Department of Oral Molecular Pathology

Tokushima University Graduate School

3-18-15 Kuramoto, Tokushima 770-8504, Japan.

E-mail: ishimaru.n@tokushima-u.ac.jp

Telephone: +81-88-6337464 Fax: +81-88-6337464