

February 22, 2014

Dear Editor,

Thank you very much for your very helpful comments and hard work on our manuscript. Please find enclosed the edited manuscript in Word format (file name: 9071-review.doc).

Title: Ulcerative colitis as a polymicrobial infection characterized by a sustained broken mucus barrier

Author: Shui-Jiao Chen, Xiao-Wei Liu, Jian-Ping Liu, Xi-Yan Yang, Fang-Gen Lu

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 9071

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

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers,

Responses to the comments of Reviewer 00503587

This manuscript reviews aspects of microbiology and the mucus layer relevant to the pathogenesis of UC. Specific Comments: 1. Overall, there are a number of sections that appear quite jumbled, with poor flow. One example is the section on bacteria in UC. Reorganisation of this (and several other sections) to ensure optimal flow and coordination of ideas and concepts is required.

Response: Thank you so much for your suggestion, and we've made corrections in the revised manuscript.

2. Further, the text comments on the destruction of mucus in one paragraph, but this is followed by a section detailing the nature of mucus and mucins: these are in the wrong order. Similarly, the nature of the intestinal microflora should be introduced before outlining changes in the flora that are noted in the context of UC.

Response: Thank you, we have made corrections according to your suggestion.

3. The initial sections of the manuscript do not refer to genetics - this is only mentioned in the last page of the manuscript. This should be reviewed also

Response: Genetics is an important element of UC, we review this in the initial sections of the revised manuscript.

4. The Introduction section refers to the DSS model of colitis. This is model of one

aspect of colitis, and the findings should be presented with more caution.

Response: Thank you, we have made corrections according to your suggestion.

5. Page 3 refers to a microbial module - it is not sure what this is?

Response: We have deleted this to avoid ambiguous understanding.

6. The authors should mention in the abstract and/or Introduction that this is review article. this is not clearly apparent.

Response: Thank you for your suggestion, we have mentioned this in revised manuscript.

7. There are errors of English word usage and grammar that require correction

Response: Thank you so much for your suggestion, and we've made corrections in the revised manuscript.

8. The references are not all in the correct format. The page numbers are not present

Response: Thank you, we have made corrections according to your suggestion.

9. The authors should consider preparing a diagram or cartoon that illustrated the key features of the work - this would greatly enhance the usefulness of this review.

Response: According to your suggestion, we added table 1 to illustrate our ideas.

Responses to the comments of Reviewer 00503405

In the review article of Chen et al. about UC as a polymicrobial infection with defected mucus barrier the authors aimed to highlight the role of luminal bacteria in the pathogenesis of UC. The review is about a clinically very important topic, contains many new information about microbiota in UC, but the most interesting thing, namely the connection of luminal pathogens to mucosal immunity is not discussed. In this issue the role of TLRs (especially TLR5 and TLR9) as a switch point between innate and adaptive immunity must be discussed. English language needs minor polishing. After major revision I suggest to accept the article for publishing in WJG.

Response: Epithelial barrier dysfunction brings about increased bacterial translocation through the lamina propria. Ineffective bacterial clearance leads to excessive toll-like receptor (TLR) stimulation, secretion of pro-inflammatory cytokines and activation of innate and T-cell mediated immune responses, and the innate and adaptive immunity play an important role in UC, we added these in our revised manuscript.

Responses to the comments of Reviewer 00034437

The authors demonstrated that polymicrobial infection characterized by sustained broken mucus barrier led to subsequent bacterial migration toward the mucosa and proliferation of complex bacterial biofilm on the epithelial surface in UC patients with human as well as animal models Major Overall, this paper is interesting, however, this reviewer would like the authors to add more basic research data regarding abnormality of goblet cells in patients with UC. For example, Hes-Notch signaling pathway plays an important role in the differentiation of goblet cells. Minor There are some wrong references. Please check it.

Response: Thank you very much. According to your suggestion, we add more basic research data regarding abnormality of goblet cells in patients with UC, and revise the references.

3 References and typesetting were corrected.

We deeply appreciate your consideration of our manuscript, and hope this paper is suitable for your journal.

Sincerely yours,

Fanggen Lu,

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