

Format for ANSWERING REVIEWERS



August 12, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4276-review.doc).

Title: Intestinal barrier: molecular pathways and modifiers
A review of the literature

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Name of Journal: *World Journal of Gastrointestinal Pathophysiology*

ESPS Manuscript NO: 4276

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

1 Format has been updated

[This is done.](#)

2 Revision has been made according to the suggestions of the reviewer

[We would like to thank the reviewers for their help in improving our manuscript. This is very much appreciated. We have changed the manuscript according to their comments.](#)

Reviewer #1

1. *Title will be modified without "The".*

[This has been corrected, thanks for this.](#)

2. *I guess that authors are interested in pathogenesis of intestinal-base immune-mediated disease, but can you describe the link between your interest and this review paper in INTRODUCTION"?*

[To address this comment we have added the following sentences to the introduction section:](#)

["Disruption of this delicate balance causes a variety of intestinal-related inflammatory and autoimmune syndromes^{\[6-8\]}. For example, healthy first degree relatives of patients with IBD and celiac disease have increased intestinal permeability and epithelial apoptosis^{9,10\]}. Intestinal barrier dysfunction also contributes to the severity of food allergen-induced clinical symptoms^{\[11\]}".](#)

[Please see the third paragraph of introduction section on page 3.](#)

Reviewer #2

1. *To the Authors In this review the Authors summarize the principal molecular signalling pathways regulating intestinal homeostasis. The concept of intestinal homeostasis is defined as the continuous replenishment of intestinal epithelium for the maintenance of its integrity, from which depends also its defensive function. The exposure and the level of deepening appear appropriate for this minireview. The introduction synthesizes clearly the topic, but the conclusions are excessively simplified and do not permit to completely appreciate the significance of the arguments. Moreover, the abstract gives rise to an expectation on "the pathogenesis of intestinal-based immune-mediated diseases", but this is not treated in the conclusion: there is only a very rapid mention at the therapy of inflammatory bowel disease, but not at the pathogenesis. I suggest to eliminate the above ambiguity.*

We have eliminated the relevant sentences as suggested and altered the conclusion to better illustrate this point "the pathogenesis of intestinal-based immune-mediated diseases". Please see the conclusion section on page 7.

2. *In my opinion, a short discussion about the disruption of the intestinal barrier and its clinical implications in the pathogenesis of disease like IBD, food allergy, celiac disease, etc., could be very interesting. While the topic are molecular pathways, a simply mention at the above clinical implications could be enough.*

Thank you for your suggestion. We agree that this would be a good idea and these have been discussed with a few more sentences in the conclusion:

"Intestinal epithelial barrier dysfunction has been implicated as a critical role in the predisposition to a number of gastrointestinal diseases such as IBD, food allergy and celiac disease. It could lead to defects in multiple aspects of microbial, epithelial, and immune interactions, and thus injury to the epithelial lining thought to be an important factor in the pathogenesis of intestinal-based immune-mediated diseases^[48-50]".

3. *Minor revision:*

- *Conclusions: where "recent studies" are cited, the corresponding bibliographic references should be indicated.*

As mentioned in comment 1 and 2 (reviewer #2), we amended the conclusion section and it is now cited in the modified section. Please see the conclusion section on page 7.

- *It should be appreciable a brief explanation of the figure.*

Thank you very much for the comment. Based on the reviewer's recommendation, we have added these sentences in the legend of figure 1 (page 8):

"Wnt signaling promotes proliferation of TA/stem cells and drives Paneth cell maturation. Notch signaling cooperates with Wnt to drive proliferation of ISCs and regulates maintenances of undifferentiated TA/stem cells. Hippo and BMP signaling inhibit proliferation and induce maturation of all secretory cell types. Hedgehog signaling activates the expression of BMP in the mesenchyme".

- *There are some mistakes in the English language.*

We have revised and corrected all those minor comments (i.e. any typing errors) raised by the reviewer. Many thanks.

3 References and typesetting were corrected

[This is done.](#)

Thank you again for publishing our manuscript in the *World Journal of Gastrointestinal Pathophysiology*

Sincerely yours,

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