



June 13, 2018

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Director, Editorial Office
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Thank you very much for the e-mail of April 04 2018 regarding the decision and referee comments of the Invited Review Manuscript (39030) "**Priming the seed: How *Helicobacter pylori* alters the invasive properties of epithelial cells in early gastric carcinogenesis**" by Silvia Molina-Castro, Vanessa Ramírez-Mayorga and Warner Alpízar-Alpízar. We are pleased by the reviewers' interest and their valuable comments to our manuscript. Accordingly, we have revised the manuscript and we are now resubmitting the revised version. We have responded in the following way to the reviewers' comments:

Reviewer: 1

Comments to the Authors

"This review summarized how *H. Pylori* alters the invasive properties of epithelial cells in early gastric carcinogenesis. The authors presented the involvement of *H. Pylori* in the acquisition of cell invasion behavior, mainly in the deregulation of molecules that control ECM remodeling, EMT, and cell polarity. However, writing is somewhat disorganized."

We have modified the organization of the section "INVASION AND METASTASIS". Specifically, we have moved the "*PA system and H. pylori*" and "*MMPs and H. pylori*" sub-sections to the end of the manuscript. Then, the "INVASION AND METASTASIS" section of the revised version is now organized as follows:

EMT and H. pylori - Cell polarity alterations induced by H. pylori - PA system and H. pylori - MMPs and H. pylori. We believe this change will improve the structure of the paper.

"1. In the HELICOBACTER PYLORI part, if the authors elucidate these bacteria structures and their encoding proteins with a figure, it will help to understand the importance of this bacteria in GC."

A new figure (Figure 1) has been added to revised version of the manuscript, as suggested by the reviewer.

"2. The authors should add another Figure to summarize different roles of *H. pylori* in these different cellular processes, such as plasminogen activation system, matrix metalloproteinases, epithelial-to-mesenchymal transition, cell polarity alterations."

A new figure (Figure 2) has been added to revised version of the manuscript, as solicited by the reviewer.

"3. It needs to improve the structure of the sentences and improve English grammar and spelling throughout."



The revised version of the manuscript was submitted to Filipodia for English polishing and we now provide a Language Certificate Letter stating that the manuscript has achieved Grade A: priority publishing; no language polishing required after editing.

Reviewer: 2

Comments to the Authors

"This work is therefore interesting, novel with merit especially related to *H. pylori* pathogenesis."

We thank the reviewer for the positive comment.

"The manuscript appears well organized and written in English, but also appears missing in-depth analysis of the selected molecules and inner link between the metastasis and mechanisms, of which important aspects are roles of epigenetics, stem cell, E-cadherin etc."

We consider that an in-depth analysis of the selected molecules and inner link between the metastasis and mechanisms is not strictly needed since this has been reviewed elsewhere. In addition, this would represent to add more text (pages) to the manuscript, and we consider it to be long enough as it is now. We, however, added a sentence in page 9 (second paragraph) of the revised version of the manuscript in which we are referring to excellent previously published reviews addressing the mechanistic details of such processes, as follows:

"The cellular and molecular mechanisms underlying these processes, as well as their regulation, have been reviewed in depth^[39, 40, 43-45]."

We hope this will solve the situation.

"A few cartoons might also be helpful, and reference appears take a too many pages. The work may require more in-depth revision to strengthen the claim, and importantly, point out directions for future investigation to guide readers and researchers."

We have added two new figures (Figures 1 and 2) to revised version of the manuscript, as suggested by the reviewer.

We consider that we have kept the number of references to the least possible and that we strictly cited the most representative and important ones. Therefore, we feel that we have been rigorous on this particular issue already.

At the end of the manuscript (page 20), in the very end of the "conclusion" section, we added two paragraphs pointing out some issues that deserve further investigation, as follows:

"Therefore, the link between *H. pylori* and cell invasive properties is complex and an exciting open area of research where many aspects remain far from being clear. For instance, there is a need to gain further insight on how and under what circumstances *H. pylori* manipulates regulatory networks controlling the EMT and stem-cell programs. Also, it is important to unravel the cellular and molecular mechanisms underlying the induction of members of the PA system and MMPs in *H. pylori*-colonized gastric epithelium."



Elucidation of the key orchestrators governing these invasion-related programs is crucial to understanding the implications that these processes may have for the survival of the bacterium or in the pathological context. All this information could be of relevance for identifying individuals with an increased risk of GC, who may require *H. pylori* eradication therapy, especially in countries with limited resources and high prevalence of this bacterial infection. Finally, this may contribute to prediction of pre-neoplastic lesions that are more likely to progress in the pathogenic series of steps to malignancy, which may be of relevance to reducing GC burden."

Reviewer: 3

Comments to the Authors

"We criticized no reference to hypergastrinemia or the use of PPI and H2-histamine blocker in the review"

We consider that this is a topic that is not strictly relevant in our manuscript and, therefore, out our scope. Although this may in an interesting topic, it is probably worth discussing in a different context, but not necessarily in a review manuscript addressing the role of *Helicobacter pylori* in the manipulation of cellular and molecular programs that lead to increased invasive behavior of the gastric epithelial cells.

We have also dealt with all aspects raised by the editor in the "39030-Edited (download)" Word file, which was downloadable from the submission website. It is important to mention, that were advised by the Language Editing Company (Filipodia) to modify a little bit the title and running title of the manuscript, in order to comply with the number of words that World Journal of Gastrointestinal Oncology requires. We, therefore, made the modifications as suggested. We then modified the title from "Priming the seed: How *Helicobacter pylori* alters the invasive properties of epithelial cells in early gastric carcinogenesis" to "Priming the seed: *Helicobacter pylori* alters epithelial cell invasiveness in early gastric carcinogenesis". Also, the running title was modified from "How *H. pylori* alters cell invasive properties" to "*H. pylori* alters cell invasive properties"

Kind regards,

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