

Manuscript 82965

Answering Reviewers

Dear Editor,

Thank you for giving us the opportunity to submit a revised draft of the manuscript "***Helicobacter pylori* plays a key role in gastric adenocarcinoma induced by spasmolytic polypeptide-expressing metaplasia**" for publication in the *World Journal of Clinical Cases*. We appreciate the time and effort that you and the reviewers dedicated to providing feedback on our manuscript. We are grateful for the insightful comments which have helped improved the quality of our paper.

We have studied all comments carefully and made changes in the manuscript. These changes have not affected flow or the framework of the paper. Below we have listed only those changes which address the reviewer's comments. In the manuscript, all changes/revisions are highlighted blue.

We would again like to express our appreciation for the Editor's and Reviewers' comments and feedback, and hope that our corrections will meet with approval.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

**Hai-Wen Li, MD,**

The main corrections in the paper and the responses to the reviewers' comments are as follows:

### **Reviewer 1**

This review article is of value because it mentions factors involved in the development and proliferation of SPEM, which is an important issue when considering intestinal metaplasia and gastric carcinogenesis. The "Conclusions" could be more compact as it is a repetition of what is stated in the text. NMMG is also an agent that induces SPEM (Yamaguchi H, et al. Lab Invest 82:1045-1052,2002).

Author response:

We thank Reviewer 1 for this insightful suggestion. As suggested, we have revised the "Conclusions", making it more concise and summarizing the central ideas of this paper (Page 15-16, Lines 429-430 and 433-443). Also, we have gone through the suggested paper (Yamaguchi H, et al. Lab Invest 82:1045-1052,2002) and have added the relevant information which reads as follows (Page 7, Line 177-179):

*"In addition, SPEM was found in a rodent animal model that had received preoperative nitrite carcinogen administration and developed post-gastrectomy syndrome."*

### **Reviewer 2**

In present review, authors shown the role of SPEM in gastric adenocarcinoma. I have several reservations; my comments are appended as below: 1. There are several pathway affecting the progression of SPEM in "SPEM is induced by the loss of parietal cells in combination with additional signals", please list a table to summarize these pathways and try to find possible potential connection among them. 2. There are many references that

have not been added in “4. The progression from normal gastric mucosa to SPEM is dynamic and consecutive”, please add. 3. Could you expand on the relationship between SPEM and macrophages? Does SPEM promote the polarization of macrophages, when? 4. Please talk about the relationship between IM and SPEM, for example, which one is more serious? Could they affect each other? etc. 5. Some references are too old, please change them. 6. Last but the most crucial opinion: the title of this review is “*Helicobacter pylori* plays a key role in SPEM-induced gastric adenocarcinoma”, you need have a clear summary about how *Helicobacter pylori* affects gastric adenocarcinoma by SPEM, please add.

Author response:

We thank Reviewer 2 for making multiple valid, helpful comments and suggestions. We have taken all these comments and suggestions into account as follows:

1. We have followed reviewer’s suggestion and have added a table (Table 2) at the end of the article, which lists all the pathways affecting the progression of SPEM mentioned in the article. We have also added this text as a summary to the Table 2 (Page 8, Lines 207-212).

“The loss of epidermal growth factor secreted by parietal cells and the inflammatory response caused by it are of special significance for the occurrence and development of SPEM. However, in the absence of enough research, the potential connection is difficult to establish and thus more studies are needed.”

2. Thank you for catching this error. We have now included the reference related to information in “4”.

3. This suggestion by reviewer will certainly help readers to have a comprehensive understanding of the relationship between SPEM and

macrophages. Thank you for this comment. We have now added the relevant information in the manuscript and it reads as follows (Page 14, Lines 388-395):

“The occurrence and development of SPEM are closely related to macrophages. Firstly, L635-treated macrophage-depleted mice demonstrated a significant reduction in SPEM cell numbers, indicating that macrophage infiltration may promote the production of SPEM cells. Secondly, after SPEM induction, WFDC2 secreted by SPEM has been confirmed to induce M2 macrophage polarization and up-regulate the secretion of IL33 by macrophages to advance SPEM.”

4. We have also added in this text following Reviewer 2's comments (Pages 5-6, Lines 137-147): “Previous studies have reported that SPEM and IM often co-exist in people with atrophic gastritis caused by chronic *H. pylori* infection<sup>[13,14]</sup>. Notably, SPEM and IM are two different lineages of metaplastic cells. SPEM are cells marked by the expression of TFF2 and MUC6, while the characteristic markers of IM are TFF3, MUC2 and CDX2<sup>[15]</sup>. The current mainstream view is that the progression of SPEM leads to IM. According to immunocytochemical evidence, SPEM expressing TFF3 and MUC2 has been reported; therefore, intermediates of intestinalized SPEM may exist that reflect evolution of metaplastic phenotypes<sup>[13]</sup>. However, one study also found MIST1 and CDX2 double positive SPEM cells, indicating that IM may not come from a single pathway of SPEM progression.”

5. As suggested by Reviewer 2, we have now removed some of the older references, but kept a few classic references that we feel must be part of our review paper.

6. As suggested, we have revised the "Conclusions" section, making it more concise and summarized the central ideas of this paper. Based on our research and the current literature that can be retrieved, we have summarized the possible connections between SPEM and *H. pylori*.