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**5<sup>th</sup> December 2013**

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6656-review.doc).

Title: "Title: Colonization and infection of the human stomach by *Helicobacter pylori*", a topic highlight and review article

Author: Ciara Dunne, Brendan Dolan, Marguerite Clyne

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6656

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

1. Reviewer 00039368

We would like to thank the reviewer for comments on our paper. We have addressed the specific points raised by this reviewer below

1. We have changed the title of the paper to reflect the manuscript content as suggested by the reviewer. The new title is "Factors that mediate colonization of the human stomach by *Helicobacter pylori*"

2. We have modified the figure to provide more detail and to demonstrate the interplay between *H. pylori* factors and the host as outlined in the text.

3. We agree with the reviewer that the mechanism of evasion of the immune response is a relevant topic. However this topic has been reviewed extensively only recently. We do not think there is the space in this review to include *H. pylori* evasion of the innate immune response in adequate detail. Therefore we have referred the reviewers to two excellent recent reviews (1. Müller A, Oertli M, Arnold IC. *H. pylori* exploits and manipulates innate and adaptive immune cell signaling pathways to establish persistent infection. Cell Commun Signal. 2011 Nov 1;9(1):25. doi: 10.1186/1478-811X-9-25. PubMed PMID: 22044597; PubMed Central PMCID: PMC3214186 and 2. Salama NR, Hartung ML, Müller A. Life in the human stomach: persistence strategies of the bacterial pathogen *Helicobacter pylori*. Nat Rev Microbiol. 2013 Jun;11(6):385-99. doi: 10.1038/nrmicro3016. Epub 2013 May 8. Review. PubMed PMID: 23652324; PubMed Central PMCID: PMC3733401).

4. We have included a short summary statement at the end of major sections as suggested by the reviewer.

Reviewer 00225338



**5<sup>th</sup> December 2013**

We would like to thank the reviewer for the comments on our paper. We have gone through the review as suggested and added references where required.

1. We have amended the statement that *H. pylori* is not found at other sites in the human body. We now state that *H. pylori* is found at sites of gastric metaplasia. (Introduction second paragraph)

2. We have amended the statement that *H. pylori* organisms living in gastric mucus serve as the reservoir of infection for the underlying organisms to reflect that it is our suggestion that these organisms act as a reservoir for infection.

3. We have amended the statement that pathogens that infect mucosal surfaces share two main goals.....It now reads "Pathogens which infect mucosal surfaces share two main goals: (1) to overcome the mucus barrier and (2) to interact with the underlying epithelial cells which results in disease.

4. When the pH gradient that exists across the gastric mucus layer was disrupted in Mongolian gerbils *H. pylori* were no longer found close to the epithelium but were scattered throughout the mucus layer, suggesting that pH plays an important role in maintaining the particular localisation of *H. pylori*.

We have now added a reference after this statement - Schreiber S, Konradt M, Groll C, Scheid P, Hanauer G, Werling HO, Josenhans C, Suerbaum S. The spatial orientation of *Helicobacter pylori* in the gastric mucus. Proc Natl Acad Sci U S A 2004; 101(14): 5024-5029 [PMID: 15044704 DOI: 10.1073/pnas.0308386101].

5. "This suggests that MUC5AC or a molecule co-expressed with it may explain the preference of *H. pylori* for gastric mucus. *H. pylori* has been shown to interact with the Lewisb blood group antigen structure found on the surface of MUC5AC in gastric mucus and binding is mediated through the bacterial outer membrane protein, BabA. Needs references - considering the ample amount of published literature of *H. pylori* binding to purified gastric mucins, I find it odd that the only ref about binding to mucins is one about in vivo colocalization with mucins - i.e. staining that shows that *H. pylori* binds to the same cells that produce mucins, although in the same compartment, there are hundreds of other molecules present that could be responsible for this "co-localization".

We agree with the reviewer that the references in this section are not adequate. We have broken this section into two paragraphs so that the end of the first paragraph reads

This suggests that MUC5AC or a molecule co-expressed with it may explain the preference of *H. pylori* for gastric mucus.

And the next paragraph starts with



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*H. pylori* has been shown to interact with the Lewisb blood group antigen structure found on the surface of MUC5AC in gastric mucus and this interaction which has been extensively studied is mediated through the bacterial outer membrane protein, BabA (Ilver D, Arnqvist A, Ogren J, Frick IM, Kersulyte D, Incecik ET, Berg DE, Covacci A, Engstrand L, Borén T. Helicobacter pylori adhesin binding fucosylated histo-blood group antigens revealed by retagging. Science. 1998 Jan16;279(5349):373-7. PubMed PMID: 9430586).

6. During chronic infection by *H. pylori*, there is an increase in the proportion of sialylated structures present in the gastric mucosa, which is attributed to mucosal inflammation and transformation[61]. These structures appear after a sustained period of infection, and so SabA is thought to play a role in promoting chronic infection.” –

We have modified the above to now read

During infection by *H. pylori*, there is an increase in the proportion of sialylated structures present in the gastric mucosa, which is attributed to mucosal inflammation and transformation[61] and so SabA is thought to play a role in promoting chronic infection.

Reviewer 00227428

We thank the reviewer for his comments and for reviewing the manuscript.

Thank you again for publishing our manuscript in the World Journal of Gastroenterology.

Sincerely yours,