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Answers to the Reviewer 00000001

1. There is a very long introductory background section (page 1-16), followed by sections on *H. pylori* diversity (page 16-24) and host genetic susceptibility and immune profile (page 24-37). The manuscript could be improved by shortening the length of the introductory section (page 1-16) to remove tangential content.

Introductory section has been shortened in the range of 1-16 pages.

2. Abstract line 11-13 states: “Due to the specific virulence factors of *H. pylori*, gastric cancer might have an asymptomatic course”. This statement is misleading. Gastric cancer is always asymptomatic in the early stages, but most experts assume that gastric adenocarcinoma always progress over time to cause symptoms if untreated.

It has been changed to: “Gastric cancer is asymptomatic in an early stages, but always progress over time to cause symptoms if untreated”.

3. Abstract line 13 states, “97% of gastric cancers are malignant”. The meaning of this statement is unclear. What type of gastric cancer is not considered malignant?

It has been changed to: “In 97% of stomach cancer cases metastasis of cancer cells to other organs occurs”.

4. Page 2, paragraph 2 states that “PAI components, toxins, adhesions...enable these microbes to colonize the stomach for a long period of time”. This statement is misleading. For example, strains that lack the PAI routinely colonize the stomach for long periods of time.

It has been changed to: “Various structural components and soluble factors of *H. pylori* enable these microbes to colonize the stomach and induce inflammatory response”.

5. Page 2, last line states that the bacteria “invade the stomach”. *H. pylori* does not typically invade host cells.

It has been removed.

6. Page 3, end of second paragraph, suggests that *H. pylori* can colonize the oral cavity. There is very little evidence to support this statement. Recommend that this statement should be deleted.

It has been deleted.

7. Page 3, last paragraph begins with question, “What makes this pathogen so dangerous to humans? This is misleading statement. Most people colonized with *H. pylori* remain asymptomatic for life.

It has been removed.

8. Page 3, last line. Is there really any evidence that OipA acts as an adhesion? The cited references (ref 8-12) do not support this statement.

It has been corrected according to the new ref. 11, which has been changed (Oleastro M, Menard A, The role of *Helicobacter pylori* outer membrane proteins in adherence and pathogenesis. Biology 2013, 2:1110-1134, DOI:10.3390/biology2031110).

Now the statement is as follows: "The role of other OMPs such as HopZ and OipA proteins as adhesions is not clear. However, it has been shown that OipA promotes more severe gastric diseases (duodenal ulcer and gastric cancer), high *H. pylori* density, and severe neutrophil infiltration"

9. Page 4, first paragraph. Is there really any evidence that Lewis-like antigens in LPS facilitate *H. pylori* adherence to gastric epithelial cells? The cited references (ref 20-22) do not support this statement.

The cited reference 22 contain the information, which confirms this statement.

It has been changed to: "It may carry various human Lewis-like antigens, which may play a role in autoimmunity and specifically LewisX determinants in O antigen of *H. pylori* LPS may facilitate the adherence of bacterial cells to gastric epithelium via β-galactoside-binding lectin (galectin-3), which has been identified as a gastric receptor".

10. Page 4, paragraph 2 describes a correlation between the presence of CagA and a higher risk of inflammation. This statement is misleading. All *H. pylori*-infected people have gastric inflammation.

It has been changed to: " The correlation between the presence of CagA in *H. pylori* strains and more severe inflammatory response or a higher risk of gastric cancer has been shown."

Ref 27 has been changed to another one, which confirms this statement (Peek RM Jr, Blaser MJ. *Helicobacter pylori* and gastrointestinal tract adenocarcinomas. Nat Rev Cancer 2002, 2: 28-37. DOI: 10.1038/ncr703).

11. Page 4, last paragraph, states that the PAI includes genes encoding VacA, BabA and SabA. This statement is incorrect. The genes encoding VacA, BabA and SabA are located outside the PAI.

It has been removed.

12. Page 5. First line states that VacA causes “elevation of the inflammatory response”. The cited reference (res 29) does not provide any strong evidence to support this statement.

The statement has been changed to: “VacA induces vacuolation of gastric epithelial cells as well as cell apoptosis and disrupts the gastric epithelial barrier function”

13. Page 5, first line, states that BabA and SabA “promote complement resistance and regulate the immune response of the host”. References to support this statement should be provided.

It has been changed to: “BabA and SabA are adhesions and SabA is essential for nonopsonic activation of human neutrophils [11]”

14. Page 5, first paragraph states that SabA recognizes LewisA antigens. SabA is known to bind sialyl-dimeric-lewisX (see Mahdavi et al., Science 2002), but is there any evidence that it binds to Lewis A? The cited reference (ref 9) does not provide support for this statement.

It has been changed according to the data provided by ref 8 and 9: “ SabA is known to bind sialyl-dimeric-Lewis X[8] as well as sialylated Lewis A [9]. Malignant transformation is linked with a pronounced expression of Lewis A, sialylated Lewis A and sialyl-dimeric-Lewis X, however the knowledge about the role of SabA in tumorigenesis is still limited [9]”.

15. Pages 7-8 describe the epidemiology of H. pylori infection. This is tangential to the man topic of the review article. Recommend that this section should be shortened substantially.

It has been shortened.

15. Page 9 describes a long list of dermatologic, cardiovascular and pulmonary illnesses. There is relatively little evidence to support the authors’ claim that these illnesses are attributable to *H. pylori*. Recommend that this section should be shortened substantially or deleted.

It has been shortened substantially.

16. Page 11, line 8 states that “97% of gastric cancers are malignant”. The meaning of this statement is unclear and no references are cited. What type of gastric cancer is not considered malignant?

It has been corrected as follows: “97% of gastric cancer cases are linked with metastasis”.

17. Page 11 presents a detailed description of the clinical features of gastric cancer and details about staging of this malignancy. Recommend that this section should be shortened substantially.

It has been shortened.

18. Page 12, paragraph 3 state....? There is no more reviewer' questions in the system.

Answers to The Reviewer 03551098

1. I recommend changing the title of the manuscript: i.g. "Host pathogen interactions in *Helicobacter pylori* related gastric cancer".

It has been changed as suggested.

2. It is better to focus on the interruption of signal transduction of host cells by CagA. Recommend ref. "Novel effects of *Helicobacter pylori* CagA on key genes of gastric cancer signal transduction: a comparative transfection study. Pathogen and Disease. 12/2014; 73(3). DOI: 10.1093/femspd/ftu021.3).

It has been added in the section CagA variation: "Vaziri et al., compared the cellular effects of two different CagA EPIYA motifs on identified signalling pathways involved in the process of gastric carcinogenesis [161a]. They investigated the effects of CagA carboxyl region variations on the transcription of genes involved in carcinogenesis of gastric epithelial cells by transfection of gastric cancer AGS cell line with the eukaryotic vector carrying the *cagA* gene: ABC and ABCCC types. They analysed 42 genes of signal transduction involved in gastric cancer on the transcription level by real-time PCR. It has been found that the CagA oncoprotein of ABCCC type can induce the intestinal metaplasia, IL-8 production by epithelial cells, dysfunction of Crk adaptor proteins, anti-apoptotic and carcinogenic effects more intensively than the CagA protein of ABC type. "

Indicated ref has been included as [161a]

3. Virulence factors section: It must be summarized.

It has been summarized.

4. Tables 1 and 2 can be omitted.

Tables 1 and 2 were removed.