38629-Answering Reviewers

Dear Dr. Ze-Mao Gong
Science Editor
World Journal of Gastroenterology

We are pleased to re-submit our revised manuscript entitled, Nucleotide-binding oligomerization domain 1 and *Helicobacter pylori* infection: A review (Manuscript NO: 38629), to the World Journal of Gastroenterology as a Minireview article. We appreciate the reviewers' comments and revised the original manuscript. In addition, we also revised the original manuscript and prepared additional files as suggested by the Science Editor. In this revision, we removed the information regarding grants supports since this is a review article but not an original article. We have highlighted the changed portions as red color in this revision. Please see our responses to reviewers' concerns. We believe that our revised manuscript is suitable for publication in the World Journal of Gastroenterology.

Sincerely yours,

Tomohiro Watanabe MD, PhD
Department of Gastroenterology and Hepatology
Kindai University Faculty of Medicine

Responses to the reviewers' comments

Reviewer #1: A well written and comprehensive review summarising the protective effect of NOD1 on gastric cancer development in H.pylori infected patients.

Reply; We appreciate this positive comment from this reviewer.

Reviewer #2: This is a good review of this topic. easy to read and broad, with adequate detail Specific Comments 1. When referencing authors and using "Smith et al", the

reference sh0uld follow immediately after the author name (e.g. Smith et al [1] 2. There are some minor errors of English language word usage/grammar.

Reply; We appreciate this positive comment from this reviewer. In this revision, we carefully read the manuscript again and corrected typo-grammatical errors. Moreover, we have also corrected the position of reference citation throughout the manuscript.

Reviewer #3: In this review, the authors suggest that Hp infection of gastric mucosa leads to activation of nucleotide-binding domain (NOD1) by the bacterium peptidoglycan, thus resulting in pro-inflammatory cytokine and chemokine production. It is a strange concept since the peptidoglycan is the cell membrane constituent of Gram-positive bacteria, while the Gram-negative bacteria, including Hp. contain the cell-membrane lipopolysaccharide (LPS) also called by some "macromolecular glycolipid". Moreover, it is well established that Hp LPS evokes the gastric mucosal pro- inflammatory events (See recent review, Inflammopharmacology, vol 25, 2017,p.415). □

Reply; This reviewer considers that lipopolysaccharide (LPS)-TLR4 rather than peptidoglycan (PGN)-NOD1 pathway plays a critical role in pro-inflammatory cytokine and chemokine production caused by *Helicobacter pylori* (*H. pylori*) infection. It is now generally accepted that mucosal host defense against *H. pylori* depends upon sensing of PGN by NOD1. Since Viala et al. identified NOD1 as a critical innate immune sensor for this organism in 2004 (ref 16, Nature Immunology), this notion has been confirmed by famous researchers. Famous immunologists and gastroenterologist (ref 16, 27, 34, 37, 39, 41, 54) published original manuscript regarding NOD1 and *H. pylori*. Thus, it is no doubt that NOD1 activation plays an important role in gastric mucosal inflammatory responses in *H. pylori* infection. However, as this reviewer points out, it is also possible that LPS-TLR4 pathway is involved in gastric mucosal inflammatory responses in addition to PGN-NOD1 pathway. To clarify this point, we revised the Introduction section and cited the reference as suggested by this reviewer (2nd

paragraph in the Introduction section, page 3).

This reviewer also points out that PGN is a cell wall component of Gram-positive, but not Gram-negative bacteria. We would like to emphasize that PGN is a cell wall component of both Gram-positive and Gram-negative bacteria. Thus, he/she appears to misunderstand this point. To clarify that H. pylori has immuno-potent PGN, we revised the manuscript (page 5-6, Type IV secretion system of *H. pylori* and NOD1 activation section).