Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road,
Wan Chai, Hong Kong, China

BAISHIDENG PUBLISHING GROUP CO., LIMITED COPYRIGHT ASSIGNMENT

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript No: 5634

Title: Novel Role of Toll like Receptors in *Helicobacter pylori*-induced gastric malignancy

Authors (typed): Uno Kaname MD, PhD, Kato Katsuaki MD, PhD, Shimosegawa Tooru Prof.

1 Statement that the manuscript is not simultaneously being considered by other journals.

2 Statement that the manuscript has no redundant publication, plagiarism, data fabrication or falsification.

3 Statement that there is no conflict of interest in the paper.

4 Statement that the experiments were done in compliance with the laws regarding the use of animals and human subjects.

5 Statement that the material contained in this manuscript is original, except when appropriately referenced to other sources, and that written permission has been granted by any existing copyright holders.

6 Statement agreeing to transfer to Baishideng Publishing Group Co., Limited all rights of the manuscript, including: (1) all copyright ownership in both print and electronic formats; (2) the right to grant permission to republish or reprint the stated material in whole or in part, with or without a fee; (3) the right to print copies for free distribution or sale; and (4) the right to republish the stated material in a collection of articles or in any other format. Articles published by this publisher are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non-commercial and is otherwise in compliance with the license.

7 Statement that there are no grammar, syntax, spelling, punctuation or logic errors.

Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road,
Wan Chai, Hong Kong, China

8 Statement that figures and tables have been correctly placed and clearly indicated.

9 Statement that references are numbered in the order they appear in the text.

All authors must sign their names separately in his/her own handwriting in the order they appear in the title page of the manuscript.

Note: Co-first author and co-corresponding author are not acceptable by our journals. And please typewrite your name with the last name in full, and the first and any middle names in abbreviation, *e.g.*, author "Eamonn M Quigley", the abbreviated name should be put as Quigley EM (Last name: Quigley; first and middle names: EM); author "Jin-Lei Wang", the abbreviated name should be put as Wang JL (Last name: Wang; first and middle names: JL).

A GENTLE REMINDER: You are recommended strongly to withdraw your paper in case of the following conditions: (1) Plagiarism; (2) Data falsification; (3) Redundant publication; and (4) Divergence about the qualification of authorship. Once the paper is published online, the author who wishes to withdraw the paper must pay 10000 USD to compensate for the loss incurred. The paper will then be withdrawn within four weeks.

1st Author

Last Name: Kaname

First Name (all in abbreviation): Uno

Signature: Kaname Uno

Date: 10/25/2013

2nd Author

Last Name: Katsuaki

First Name (all in abbreviation): Kato

Signature: Katsuaki Kato

Date: 10/26/2013

3rd Author

Last Name: Tooru

First Name (all in abbreviation): Shimosegawa

Signature: Tooru Shimosegawa

Date: 10/27/2013

4th Author

Last Name:

First Name (all in abbreviation):

Signature:

Date:

5th Author

Last Name:

First Name (all in abbreviation):

Signature:

Date:

Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road,
Wan Chai, Hong Kong, China

BAISHIDENG PUBLISHING GROUP CO., LIMITED COPYRIGHT ASSIGNMENT

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript No: 5634

Title: Novel Role of Toll like Receptors in *Helicobacter pylori*-induced gastric malignancy

Authors (typed): Uno Kaname MD, PhD, Kato Katsuaki MD, PhD, Shimosegawa Tooru Prof.

1 Statement that the manuscript is not simultaneously being considered by other journals.

2 Statement that the manuscript has no redundant publication, plagiarism, data fabrication or falsification.

3 Statement that there is no conflict of interest in the paper.

4 Statement that the experiments were done in compliance with the laws regarding the use of animals and human subjects.

5 Statement that the material contained in this manuscript is original, except when appropriately referenced to other sources, and that written permission has been granted by any existing copyright holders.

6 Statement agreeing to transfer to Baishideng Publishing Group Co., Limited all rights of the manuscript, including: (1) all copyright ownership in both print and electronic formats; (2) the right to grant permission to republish or reprint the stated material in whole or in part, with or without a fee; (3) the right to print copies for free distribution or sale; and (4) the right to republish the stated material in a collection of articles or in any other format. Articles published by this publisher are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non-commercial and is otherwise in compliance with the license.

7 Statement that there are no grammar, syntax, spelling, punctuation or logic errors.

November 5th, 2013

Dear Editors of *World Journal of Gastroenterology*,

Please find enclosed the edited manuscript in Word format (Uno Revised version: 5436-review.doc).

Title: Novel Role of Toll like Receptors in *Helicobacter pylori*-induced gastric malignancy

Author: Uno Kaname MD, PhD,[1] Kato Katsuaki MD, PhD,[2] Shimosegawa Tooru Prof.[1]

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5436

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

2 Revision has been made according to the suggestions of the reviewer

Reviewer 1 (02536230)

(1) As suggested, we added the sentences in the introduction, as follows. "In this review, we aim to clarify recent discoveries in a role of pattern recognition systems in the innate immunity against *H. pylori*-related carcinogenesis."

(2) As suggested, we study previous studies of TLRs and confirm that thirteen TLRs have been discovered, 10 of which have been identified in humans so far (Nat Rev Immunol. 2013 Aug;13(8):551-65. doi: 10.1038/nri3479. Broz P, Monack DM, Newly described pattern recognition receptors team up against intracellular pathogens.)". Based on these papers, we changed sentence, as follows, "Although thirteen TLRs have been discovered in mammalian, ten types of TLRs have been identified in humans."

(3) As suggested, we added a diagram of the roles of TLRs in H.pylori-induced innate immunity (Figure2).

(4) As suggested, we added a sentence in the head of "Gene polymorphisms of TLRs in gastric cancer", as follows, "H. pylori is a major cause of gastric cancer, but only 1%–2% of H. pylori-infected individuals develops gastric cancer. [62] Recently a meta-analysis of large population-based cohort studies in Europe revealed an association between a variation of TLR1 genetic loci (4p14) and H. pylori seroprevalence. [63] The study was conducted on white populations, therefore some sample bias should be considered on different races. However, the polymorphisms of TLRs might play an important role in modulation of the direction and magnitude of the host response against the infection. This might also encourage a possible link between genetic polymorphisms of TLRs and H.pylori-associated carcinogenesis. Recent studies revealed the presence of SNPs of TLRs and their relationships with gastric cancer development (Table2). However, implications of single-nucleotide polymorphisms (SNPs) in genetic function have not been fully clarified."

Reviewer 2 (00039368)

(1) As suggested, we added the sentences in the figure legends, as follows. "Figure 1: intracellular signal propagation of human TLRs and corresponding ligands in innate immunity. TLRs and ligands in human are revealed in the figure. Individual TLRs recognize specific PAMPs or DAMPs of corresponding ligands. TLR signaling is propagated by activation of its cytoplasmic TIR (Toll/IL-1 R) domain and cooperation with various adaptor molecules, such as MyD-88, TIRAP, TOLLIP, IRAK, TRAF, TRIF, and TRAM (abbreviations are summarized below). TLR signaling consists of two distinct pathways with MyD-88-dependent and independent fashions. 1) MyD-88-dependent pathway: The MyD88 dependent pathway is down-stream of TLR1, TLR2, TLR4, TLR5, TLR6, TLR7 and TLR9. This pathway leads to the production of proinflammatory cytokines and is triggered by the association of activated TIR domain and MyD-88, recruitment of IRAK1, IRAK4 and TRAF6 to TLR-MyD-88 complex and consequent phosphorylation of IRAK1 and TRAF6. The signal is propagated by these phosphorylated adaptor molecular complex to the down-stream MAP kinases-AP1 and IKK complex-NF-κB. 2) MyD88-independent pathway: This is associated with the induction of INF-beta mediated by TLR3 or TLR4 activation. Intracellular signaling via MyD-88 independent pathway is propagated by the action of TRIF and TRAM as adaptor molecules. The signal consequently activates IKK pathway to produce INF-beta."

Reviewer 3 (01002233)

(1) As suggested, we revised the sentences and added the reference, as followed, "the stomach originally lacks intraepithelial T lymphocytes and a coordinating lymph system. [10]"

(2) As suggested, we added the legends to make sure their roles, as follows. "Figure 1: intracellular signal propagation of human TLRs and corresponding ligands in innate immunity

(3) TLRs and ligands in human are revealed in the figure. Individual TLRs recognize specific PAMPs or DAMPs of corresponding ligands. TLR signaling is propagated by activation of its cytoplasmic TIR (Toll/IL-1 R) domain and cooperation with various adaptor molecules, such as MyD-88, TIRAP, TOLLIP, IRAK, TRAF, TRIF, and TRAM (abbreviations are summarized below). TLR signaling consists of two distinct pathways with MyD-88-dependent and independent fashions. 1) MyD-88-dependent pathway: The MyD88 dependent pathway is down-stream of TLR1, TLR2, TLR4, TLR5, TLR6, TLR7 and TLR9. This pathway leads to the production of proinflammatory cytokines and is triggered by the association of activated TIR domain and MyD-88, recruitment of IRAK1, IRAK4 and TRAF6 to TLR-MyD-88 complex and consequent phosphorylation of IRAK1 and TRAF6. The signal is propagated by these phosphorylated adaptor molecular complex to the down-stream MAP kinases-AP1 and IKK complex-NF-κB. 2) MyD88-independent pathway: This is associated with the induction of INF-beta mediated by TLR3 or TLR4 activation. Intracellular signaling via MyD-88 independent pathway is propagated by the action of TRIF and TRAM as adaptor molecules. The signal consequently activates IKK pathway to produce INF-beta."

(3) As suggested, we revised the sentences, "Contrary to expectations, H. pylori-LPS is a weak stimulus of the immune response in comparison to LPS from other gram-negative bacteria owing to the unique structure of lipid core A of H. pylori-LPS [35, 36]."

(4) As suggested, we added a reference.

(5) As suggested, we revised sentences by native English speaker, as follows. "H. pylori is a major cause of gastric cancer, but only 1%–2% of H. pylori-infected individuals develops gastric cancer. [62] Recently a meta-analysis of large population-based cohort studies in Europe revealed an association between a variation of TLR1 genetic loci (4p14) and H. pylori seroprevalence. [63] The study was conducted on white populations, therefore some sample bias should be considered on different races. However, the polymorphisms of TLRs might play an important role in modulation of the direction and magnitude of the host response against the infection. This might also encourage a possible link between genetic polymorphisms of TLRs and H.pylori-associated carcinogenesis. Recent studies revealed the presence of SNPs of TLRs and their relationships with gastric cancer development (Table2). However, implications of single-nucleotide polymorphisms (SNPs) in genetic function have not been fully clarified."

(6) We are sorry, and we ask another native English speaker to revise our manuscript.

3 References and typesetting were corrected

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

Sincerely yours,

Kaname Uno

Kaname Uno
Tohoku University, Division of Gastroenterology
Kaname@wa2.so-net.ne.jp
Address; Seiryo-cho, Aoba-ku, Sendai, Miyagi, 981-8574, Japan

Kato Katsuaki

Katsuaki Kato
Miyagi Cancer Society, Center of cancer screening
kkato@cat-v.ne.jp
Address; 5-7-30, Kamisugi, Aoba-ku, Sendai, Miyagi, 980-0011 Japan
Tel; +81 22-263-1525