Reply to Pachathundikandi and Backert

TO THE EDITOR—We thank Pachathundikandi and Backert [1] for their comments on our article. We agree that their data supports our study conclusions. Their data give us new suggestions to investigate Toll-like receptor 10 (TLR10) functions. Little had been known about the function of TLR10 when we started to explore the relationship between TLR10 and Helicobacter pylori infection. Recently, several studies [2, 3] showed the relationship; however, these were clinical studies analyzing the single-nucleotide polymorphisms. Therefore, it was necessary to analyze ligands of TLR10, and we found that H. pylori lipopolysaccharide (LPS) was a ligand candidate of TLR10.

Since the discovery of TLRs, it has been revealed that innate immune responses are an important defense against pathogens; for example, intestinal mucosal cells function to protect the host from infection
with enteric bacteria [4]. By using NCI-N87 epithelial cells, we also found that *H. pylori* infection increased the expression of TLR10 messenger RNA (mRNA), because TRL10 was mainly stained on gastric epithelial cells by immunohistochemical analysis.

We also measured mRNA levels by real-time polymerase chain reaction, using THP-1 cells, and obtained results (data not shown) similar to those reported by Pachathundikandi and Backert [1]. They confirmed that TLR10 expression was observed in immune cell lines. Generally, TLR mRNAs are upregulated by stimulation with TLR ligands. They showed the same response occurred in epithelial cells and hematopoietic cells with *H. pylori* infection. Although we did not measure protein production, they confirmed that the functional activation of TLR10 signaling was associated with IRAK1 phosphorylation. These data complement our own.

They also showed that interleukin 1β (IL-1β) mRNA levels were upregulated by *H. pylori* in HEK-TLR2 cells. IL-1β is a central mediator of innate immunity and inflammation [5]. IL-1 plays a key role in the differentiation and function of polarized innate and adaptive lymphoid cells. The canonical TIR domain present in signaling receptors of the IL-1 family is shared by TLR.

We wondered about the immune response by TLR10 ligand. Shi et al [6] indicated that different ligands induce different cytokine expressions (eg, LPS induces interleukin 6 and interleukin 12p70 and polyinosinic-polycytidylic acid induces interferon-α); however, there were no data on cytokine expression stimulated by TLR10 ligand. We thought that an important point was dimerization. TLR2 families exist separately from each other. However, when ligands come, TLR2 and TLR1/TLR6 form a heterodimer and change the structure of TIR dimer and induce an immune response [7]. Almost all experiments were done by using HEK cells, and they expressed endogenous levels of TLR1, TLR6, and TLR10. Therefore, we cannot ignore the effects of TLR1, TLR6, and TLR10 when we use HEK-TLR2 cells. It is still controversial whether TLR2 forms homodimers or homodimers. There are reports [7,8] in which structure analysis showed that TLR2 forms heterodimers with TLR1/TLR6, but no studies have shown by crystal analysis that TLR2 forms homodimers. It was expected that TLR10 forms heterodimers with TLR2 [9]. TLR10 shows a very similar structure to TLR1 and TLR6 and was located on the same chromosome. TLR1 and TLR6 form heterodimers with TLR2. TLR2/TLR1 and TLR2/TLR6 recognize tri-acyl and di-acyl lipopeptide, respectively. They can distinguish acyl chain number by changing their TLR2 partner.

The reasons for this are considered to be gene duplication for coevolution between bacteria and the host immune response [10]. Our data suggested that the tetra-acyl chain is a ligand of the TLR2 and TLR10 heterodimer.

Interestingly, it has been reported that the TLR1-TLR6-TLR10 locus (4p14) is under strongly positive selection in various diseases [11]. These results provide a remarkable example of a selective advantage provided by variation in the TLRs to both human and nonhuman primates. It has been described that the TLR1-TLR6-TLR10 locus expresses individual and local differences in various diseases [12–14]. It is worth investigating the function of the TLR1-TLR6-TLR10 locus in diseases related to *H. pylori* infection.

**Notes**

**Financial support.** This work was supported by the National Institutes of Health (grant DK62813); the Ministry of Education, Culture, Sports, Science, and Technology of Japan (grants in aid for scientific research 25293104, 2640114, and 15H02657 to Y. Y.); and the Japan Science and Technology Agency (Strategic Funds for the Promotion of Science and Technology to Y. Y.).

**Potential conflict of interest.** Both authors: No reported conflicts. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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**References**


