Augmentation of *Helicobacter pylori* urease activity by its specific IgG antibody: implications for bacterial colonization enhancement

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ABSTRACT

Gastric colonization of *Helicobacter pylori* (*H. pylori*) occurs in a very early age via infected mothers having *H. pylori*-specific IgG antibodies that would be transplacentally transferred to infants. In addition, *H. pylori* urease-specific IgG was associated with chronic gastric atrophy and post-immunization gastritis is usually correlated with a strong local IgG response. These findings indicate that *H. pylori*-specific IgG antibodies, in particular its urease-specific IgG, may induce unfavorable influence on host resistance against *H. pylori*. Here, we show that we have found a unique *H. pylori* urease-specific IgG monoclonal antibody (MAb), termed S3, recognizing the conformational structure of the small subunit Ure-A, which enhanced the urease enzymatic activity. Such enhancement of the *H. pylori* urease activity induced by 1 μg of S3 was almost completely cancelled by simultaneously added the same amount of L2 MAb, which has a strong and specific inhibitory activity against *H. pylori* urease and recognizes a linear epitope of 8-mer peptide (F8: SIKEDVQF) within its large subunit Ure-B (Infect. Immun. 69 : 6597, 2001). Intravenous pre-administration of purified S3 into BALB/c mice showed significant augmentation for gastric colonization with the susceptible strain Sydney Strain-1 (SS-1). To our knowledge, this is the first demonstration that a *H. pylori* urease-specific IgG MAb induced an augmentation of their gastric colonization *in vivo*.

*Helicobacter pylori* (*H. pylori*), a gram-negative spiral bacterium, colonizes the gastric mucosa and induces various gastric diseases such as chronic gastritis, peptic ulcers, gastric cancers, and MALT lymphomas (4, 17). Although *H. pylori* infection is rare in developed countries, a high incidence of infection is commonly observed in developing countries during childhood (25). Indeed, it has been reported that *H. pylori* colonization occurs at a very early age like infancy via infected mothers (5, 14). Those infected mothers generally produce *H. pylori*-specific IgG antibodies that would be transplacentally transferred to infants. Nevertheless, *H. pylori* infection is somehow established in the infants, indicating that transplacentally acquired specific IgG antibodies do not generally protect infants from colonization by *H. pylori* (5).

In our previous work, we found that *H. pylori* urease is a major target for immune responses in patients with various gastroduodenal diseases (13) and its urease-specific IgG seems to be associated with chronic atrophic changes within the gastric mucosa (12), suggesting that some *H. pylori*-specific IgG
may cause detrimental effects on the gastric mucosa. Also, the fact that post-immunization gastritis, seen in well-protected mice, is usually correlated with a strong local IgG response in the gastric mucosa (24) reveals the unfavorable effect of humoral immunity against *H. pylori*. In addition, it has been shown that *H. pylori*-specific circulating antibodies failed to protect against *H. pylori* infection (9). Moreover, B-cell deficient mice were fully protected by challenging with *H. pylori* (3). Taken together, the above findings strongly suggest that *H. pylori*-specific humoral immunity, in particular its urease-specific IgG, may have an unfavorable influence on host resistance against *H. pylori* infection and cause disease progression.

Such predominance of humoral immunity would reduce the protective capacity against *H. pylori* infection. Actually, the *H. pylori*-induced chronic gastritis was significantly augmented not only in interferon gamma (IFN-γ)-deficient but also in IL-12-deficient mice with enhanced humoral immunity of Th2 dominancy when compared with the wild type (WT) (18). Also, a strong over-colonization was observed in the IL-12-deficient BALB/c mice (23). In contrast, the chronic gastritis would not be enhanced, but rather weakened in IL-4 deficient mice with an enhanced cellular immunity to Th1 dominancy (1). These findings indicate that Th2-dominancy with a high productivity of antibodies may induce a higher susceptibility to *H. pylori* infection in the gastric compartment.

*H. pylori* urease expressing on the very surface area among the bacterial component seems to be an important virulence factor for the colonization on gastric mucosa (7). We have reported that an IgG monoclonal antibody (MAb) against *H. pylori* urease, termed L2, recognizing a linear epitope within the large subunit of UreB, strongly inhibited its enzymatic activity, whereas urease-specific polyclonal IgG antibodies generated by immunization with purified urease protein did not induce this inhibitory effect at all (16, 21). The results suggest that there must be another type of urease-specific IgG that cancels the inhibition by augmenting its enzymatic activity.

In the present study, based on that speculation, we have examined a number of *H. pylori* urease-specific MAbs and found a unique IgG, termed S3, recognizing the conformational structure of the urease small subunit Ure-A, which showed the enhancement for urease enzymatic activity. After confirming that the S3 MAb did not cross-react with other ureases such as jack bean or *Proteus Mirabi-

MATERIALS AND METHODS

Mice. Six- to eight-week-old female BALB/c mice were purchased from Nisseizai (Tokyo, Japan) and maintained in micro-isolator cages under pathogen-free conditions. Animals were fed autoclaved laboratory chow and water. All animal experiments were performed according to the guidelines of the NIH Guide for the Care and Use of Laboratory Animals and approved by the Review Board of Nippon Medical School.

Bacteria. *H. pylori* Sydney Strain-1 (SS-1) was cultured on Brain Heart Infusion agar (Oxoid, Hampshire, UK) containing 7% heat-inactivated horse blood for 2 days at 37°C under microaerophilic conditions (5% O₂, 15% CO₂, and 80% N₂) using AnaeroPack Campylo (Mitsubishi Gas Chemical Co., Inc., Tokyo, Japan). Then, the single emerged colony was inoculated into 10 ml of Brain Heart Infusion medium (Oxoid) containing 5% inactivated horse serum, and further cultured for 24 h at 37°C under the same conditions with shaking (70–80 rpm). After the incubation, 500 μl of incubated medium containing the cells was plated on Brain Heart Infusion agar containing 7% inactivated horse blood (Nisseizai) and cultured for an additional 3 days at 37°C in a microaerophilic atmosphere. The grown bacterial cells were harvested and washed twice with cold phosphate buffered saline (PBS) at pH 7.0. Then, the cells were sedimented by centrifugation (5,000 g for 10 min at 4°C), and the cell pellet was stored at −80°C.

Purification of *H. pylori* urease. To obtain purified *H. pylori* urease, the stored bacterial cell pellet was thawed, vortexed and centrifuged at 10,000 g for 20 min at 4°C with PBS. The supernatant was harvested and transferred in a column packed with Cellulose sulfate (Millipore, Billerica, MA) made from heparin-agarose, to which the *H. pylori* urease
should be attached. Then, the attached urease was eluted with 10 ml of PE buffer (20 mM phosphate buffer and 1 mM EDTA) (pH 6.5) and fractionated into 10 tubes. Each obtained tube was examined for its urease activity against urea to select positive ones, which were then adjusted to pH 5.5 and loaded to another column with Cellufine sulfate. The loaded column was again eluted with 20 ml of PE buffer (20 mM phosphate buffer containing 0.15 M NaCl) (pH 7.4) and further fractionated into another 10 tubes to obtain purified \textit{H. pylori} urease. The purified urease protein concentration was estimated using Micro BCA Protein Assay Reagent Kit (Pierce Co., Inc., Rockford, IL) and the enzymatic activity of \textit{H. pylori} urease in each fractionated tube was measured as follows.

\textit{Measurement of H. pylori urease enzymatic activity.} Twenty-five μl of the purified \textit{H. pylori} urease was incubated with the same volume of 500 mM urea, 0.02% phenol red, and 0.1 mM DL-dithiothreitol (DTT) (Sigma Chemical, St. Louis, MO) in flat-bottomed 96-well plates. The color development was monitored at 540 nm with a microplate reader (Model 3550; Bio-Rad, Hercules, CA) at room temperature.

\textit{Western blotting.} Sodium dodecyl sulfate polyacrylamide gel (SDS-PAGE) was blotted onto nitrocellulose-polyvinylidene difluoride (Atto Co., Inc., Tokyo, Japan). The nitrocellulose blots were blocked with 25% Block Ace (Dainihon Seiyaku, Osaka, Japan) in Tris-based solution (TBS) (2 M Tris (pH 8.0), 5 M NaCl, 10% Tween 20) and incubated with murine \textit{H. pylori} urease-specific various MAbs as described previously (16, 21). The blots were washed three times with blotting buffer (2 M Tris (pH 8.0), 1.43% glycine, 5% methanol) and incubated with peroxidase-conjugated goat anti-mouse IgG 1:500 in PBS with 10% Block Ace for 1 h at 37°C. After washing three times, the blots were detected with substrates such as tetramethyl benzidine (Vector Laboratories, Burlingame, CA) and hydrogen peroxidase.

\textit{Measurement of H. pylori urease- or peptide-specific antibody titers by ELISA.} A series of nested peptides or purified \textit{H. pylori} urease antigen (5 μg/ml of each) was diluted in 0.1 mM potassium carbonate buffer (pH 9.6). Fifty μl of each diluted solution was added to wells of flat-bottomed 96-well plate (Nunc, Roskilde, Denmark), incubated overnight at 4°C and washed three times with washing buffer (PBS containing 0.05% Tween 20). After 1 h blocking with 25% Block-Ace (Dainihon Seiyaku), 50 μl of purified MAbs in PBS containing 10% Block Ace was plated for 1 h at 37°C followed by extensive washing with washing buffer, 50 μl of biotin-conjugated goat anti-mouse IgG (1:1000 dilution; Zymed, San Francisco, CA) was added, and incubated for 1 h at 37°C. After washing three times, 100 μl of an appropriate diluted class-specific (IgG) streptavidine-conjugated goat anti-mouse immunoglobulin (1:2000 dilution; Caltag Laboratories, Burlingame, CA) was added for an additional 0.5 h at 37°C. The activity of streptavidine bound to the well was determined by measuring the absorbance of ABTS (2,2′-amino-bis (3-ethylbenzothiazoline-6-sulfonic acid) di-ammonium salt) (Sigma) derived green-product at 415 nm with a microplate reader (Bio-Rad).

\textit{Effect of H. pylori urease-specific MAbs on urease enzymatic activity.} The effect of \textit{H. pylori} urease-specific MAbs on enzymatic activities of various kinds of ureases was determined by the similar procedure as measurement of urease enzymatic activity as described above. In brief, 25 μl of purified \textit{H. pylori} urease was incubated overnight with 25 μl of urease-specific MAbs in flat-bottomed 96-well microtiter plates at 4°C, and then 50 μl of 50 mM phosphate buffer (pH 6.8) containing 500 mM urea, 0.02% phenol red, and 0.1 mM DTT was added to each well. The color development was measured at 540 nm.

\textit{Assessment of H. pylori (SS-1) colonization onto the gastric mucosa of the mouse.} Two to four weeks after the challenge of SS-1 orally, BALB/c mice were sacrificed by cervical dislocation and gastric tissue was collected for the assessment of gastric colonization based on the procedure as described recently (22). The longitudinal segments of gastric tissue were homogenized in 1 ml of Brain Heart Infusion agar containing 7% inactivated horse blood, and replicate serial 10-fold dilutions were plated on \textit{Helicobacter}-selective Supplement (Oxoid). The plates were incubated at 37°C for 5 days under microaerophilic conditions and the CFU was quantified.

\textit{Statistical analysis.} The statistical significance was scored according to Student’s \textit{t}-test. The predetermined upper limit of probability for statistical significance was \(p < 0.05\).
RESULTS

Enhancement of the \textit{H. pylori} urease enzymatic activity by its specific MAb

We have previously reported that we obtained a number of murine hybridomas producing \textit{H. pylori} urease-specific MAbs from BALB/c mice immunized with purified \textit{H. pylori} urease (21). Because \textit{H. pylori} urease is composed of two subunits, a small subunit Ure-A (29.5 kDa) and a large subunit Ure-B (66 kDa), these urease-specific MAbs were classified into two groups such as Ure-A- and Ure-B-specific MAbs. Among those antibodies, we selected three Ure-A-specific MAbs, termed S2, S3 and S4, and the same number of Ure-B-specific MAbs, L2, L3 and L4, for purification and testing their ability to neutralize \textit{H. pylori} urease activity. To carry out the neutralizing experiment, we firstly confirmed their specificities to \textit{H. pylori} urease by western blotting analysis using purified urease protein (Fig. 1).

As has already described, only L2 showed strong and specific neutralizing activity against \textit{H. pylori} urease (16, 21). By screening a panel of overlapping synthetic peptides covering the whole sequence of Ure-B, we identified the minimal linear epitope for L2 as an 8-mer peptide (F8: SIKEVQF) (16). Here, we happened to find that the Ure-A-specific MAb, S3, significantly enhanced the enzymatic activity of \textit{H. pylori} urease in a dose-dependent manner (Fig. 2A), although other MAbs did not show the similar enhancement at all (data not shown). Then, we examined whether the enhancement by S3 might be abrogated when the inhibitory neutralizing MAb, L2, was added simultaneously. As demonstrated in Fig. 2B, enhancement of the \textit{H. pylori} urease activity induced by 1 μg of purified S3 was almost completely cancelled by exogenously added 1 μg of purified L2. However, the L2 MAb did not abrogate the S3-mediated augmentation when added after the overnight incubation of S3 and \textit{H. pylori} urease at 4°C (data not shown), suggesting that the enhancement of enzymatic activity mediated through S3 may be competitively inhibited by L2 MAb.

Epitope mapping of the \textit{H. pylori} urease-specific MAb (S3).

Because S3 recognized the small subunit of \textit{H. pylori} urease specifically, we then tried to identify the epitope using a series of synthetic overlapping peptides.

Table 1 A series of overlapping synthetic peptides covering entire sequence of Ure-A

<table>
<thead>
<tr>
<th>Peptide No.</th>
<th>Residues</th>
<th>Peptide Sequences</th>
</tr>
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<tbody>
<tr>
<td>UA-1</td>
<td>1-20</td>
<td>MKLTPKELDKMLHYAGELA</td>
</tr>
<tr>
<td>UA-2</td>
<td>11-30</td>
<td>LMLHYAGELAKRKKEKSKIKL</td>
</tr>
<tr>
<td>UA-3</td>
<td>21-40</td>
<td>KKRKEKIKLNVEALISIS</td>
</tr>
<tr>
<td>UA-4</td>
<td>31-50</td>
<td>NYVEVAAVEHISAKIMI</td>
</tr>
<tr>
<td>UA-5</td>
<td>41-60</td>
<td>AHIMEERARGKKTAAELMQE</td>
</tr>
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<td>UA-6</td>
<td>51-70</td>
<td>KKKAESLMQERGLKKPDDV</td>
</tr>
<tr>
<td>UA-7</td>
<td>61-80</td>
<td>GRTLLKPDVMDGVASMIHE</td>
</tr>
<tr>
<td>UA-8</td>
<td>71-90</td>
<td>MDGVASMIHEVQGEAMFPGD</td>
</tr>
<tr>
<td>UA-9</td>
<td>81-100</td>
<td>VQGEAMFPGDGFKLTVHTP</td>
</tr>
<tr>
<td>UA-10</td>
<td>91-110</td>
<td>TKLVTVHPTEANGKLVPGE</td>
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<td>UA-11</td>
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<td>171-190</td>
<td>GTAVRFEPGEEKSVELDIG</td>
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</tr>
<tr>
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<td>201-220</td>
<td>LVQADNESKIALHRAKE</td>
</tr>
<tr>
<td>UA-22</td>
<td>211-230</td>
<td>KKIALHRAKERVGFNGAKSIDD</td>
</tr>
</tbody>
</table>
peptides covering the entire sequence of Ure-A shown in Table 1. As far as we have examined intensely, we could not find any corresponding linear epitope within Ure-A (Fig. 3), although S3 strongly reacted with purified \textit{H. pylori} urease. Therefore, S3 MAb may recognize a discontinuous conformational 3-D structure but not the linear epitope within Ure-A.

The enhancement induced by S3 was \textit{H. pylori} urease-specific

Next, to confirm whether such enhancement by S3 MAb was \textit{H. pylori} urease specific, we tested the effect of S3 on Jack-Bean urease activity and found no enhancement (Fig. 4). Thus, the enhancing effect induced by S3 is specific for \textit{H. pylori} urease. Also, we have confirmed that S3 did not augment the enzymatic activity of purified \textit{Proteus mirabilis} urease at all (data not shown). These results indicate that the enhancing effect of S3 MAb is highly specific and will not affect ureases released by other commensal bacteria existing in the gastro-intestinal tract,
and thus we could see the \emph{H. pylori}-specific enhancing effect of S3 \emph{in vivo}.

\textbf{Establishment of the \emph{H. pylori}-susceptible mouse model}

To examine the effect of S3 MAb \emph{in vivo}, we established a well-characterized mouse model using BALB/c mice and pathogenic \emph{H. pylori} strain, SS-1, as described in the Materials and Methods section. As demonstrated in Fig. 5, when BALB/c mice were administrated with more than $1 \times 10^6$ CFU of SS-1 orally, the colonization of \emph{H. pylori} around $1 \times 10^6$ CFU was constantly observed in the whole gastric mucosal tissue after 2 to 4 weeks of administration. However, if less than $1 \times 10^5$ CFU of SS-1 was challenged orally, we were not able to detect any measurable colonization of bacteria in the gastric mucosa and, if mice were inoculated with $1 \times 10^5$ CFU of SS-1 orally, the results were variable. Thus, the magnitude of the attachment to murine gastric mucosa was determined by the amount of inoculated bacteria.

\textbf{Effect of intravenous administration of S3 on the gastric colonization of SS-1}

Based on the findings shown above, we then investigated to see whether the attachment of \emph{H. pylori} to gastric epithelial cells was enhanced by the intravenous inoculation of S3 MAb, which we have confirmed to be secreted from the gastric mucosa by ELISA using purified \emph{H. pylori} urease as an antigen (data not shown). As expected, when 100 μg of S3 MAb was injected intravenously 24 h before challenging $1 \times 10^6$ CFU of SS-1 orally, at least one log enhancement of the attachment in the whole gastric mucosa was usually observed in comparison with untreated controls or controls injected with the same amount of isotype matched MAb (Fig. 6).

\textbf{DISCUSSION}

In the present study, we found that a unique MAb, termed S3, enhanced the enzymatic activity of \emph{H. pylori} urease in a highly specific manner and intravenous pre-administration of S3 did enhance the colonization of \emph{H. pylori} onto gastric mucosa. This might be because the augmentation of urease activity would make a better environment for bacterial

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{To examine whether \emph{H. pylori} urease-specific S3 MAb has the capacity to enhance enzymatic activity of purified urease from other species in addition to the \emph{H. pylori}, purified urease of Jack Bean was obtained by the same purification method as described above. The distilled urease of either \emph{H. pylori} or Jack Bean was incubated overnight with 1 μg/well of purified S3 MAb at 4°C on 96-well microplates. After the incubation, phosphate buffer containing urea, phenol red, and DTT was added and optical density at 540 nm was measured. MAb S3 did not enhance the enzymatic activity of purified Jack Bean urease. Data shown are representative of three distinct experiments.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Effect of the amounts for orally administrated \emph{H. pylori} (SS-1) on its colonization onto the gastric mucosa of BALB/c mice. Two to four weeks after the challenge of SS-1 orally, the gastric tissue of each mouse was collected for the assessment of gastric colonization. As described above, the longitudinal segments of gastric tissue were homogenized in 1 ml of Brain Heart Infusion agar containing 7% inactivated horse blood, and replicate serial 10-fold dilutions were plated on \emph{Helicobacter}-selective Supplement. The plates were incubated at 37°C for 5 days under microaerophilic conditions and the appeared CFU was quantified. When BALB/c mice were administrated with more than $1 \times 10^6$ CFU of SS-1 orally, the colonization of \emph{H. pylori} around $1 \times 10^5$ CFU was constantly observed in the whole gastric mucosal tissue after 2 to 4 weeks of administration. Each dose of administration was examined in at least 3 mice for each experiment. Data shown are mean ± SD and are representative of three independent experiments.}
\end{figure}
Augmentation of Hp-urease activity by specific IgG

survival by hydrolyzing urea in the acidic gastric juice more efficiently to increase its pH. Also, the enhancement of the urease activity on the surface of H. pylori by binding with pre-administrated S3 MAb secreted from gastric mucosa may augment the ability to colonize onto the gastric mucosa through association with the class II MHC molecules expressed on the gastric epithelial cells (10, 11). Indeed, there are a number of reports showing that H. pylori urease expressing outside of the bacteria appears to be a critical factor for adhering to the gastric mucosa and urease-negative H. pylori strains as well as the urease mutants failed to colonize the gastric compartment (6, 8).

We have previously reported that H. pylori urease-specific MAb L2, recognizing a linear epitope within the UreB site, strongly inhibited its enzymatic activity (16), whereas urease-specific polyclonal IgG antibodies elicited by immunization with purified urease protein did not induce the inhibitory effect at all (21). From these observations, we speculated that there might be two types of H. pylori urease-specific antibodies; one may help to generate unfavorable gastric disorders, and the other may be beneficial in preventing bacterial growth and colonization. As demonstrated here, we found a MAb, termed S3, recognizing the conformational structure of the small subunit of H. pylori urease, showed a disadvantageous effect on preventing H. pylori infection. The former linear epitope for L2 recognition turned out to be an active site for H. pylori urease (15) and thus, L2 MAb may be able to inhibit the enzymatic activity by covering the active site. Although the actual reason for augmentation of the enzymatic activity of H. pylori urease by S3 remains to be elucidated, the fact that such inhibitory activity induced by L2 MAb was completely cancelled by externally added S3 MAb suggests that the effect of S3 may also affect the active site via an indirect mechanism through Ure-A signaling.

Although there are a number of reports showing the inhibitory effect of enzymatic activity by antibodies, very few reports have demonstrated a similar enhancing effect. Kopec et al. have recently reported that the enzymatic activity of glucosyltransferase (GTF), produced by mutans streptococci, which induces dental caries via forming of biofilm known as dental plaque, was enhanced GTF-specific IgG (19). In that paper they showed that such enhancement induced by the specific IgG was dominantly observed when GTF was expressed on the surface of the bacteria, similar to the urease of H. pylori, and referred that the specific IgG may influence on the GTF glucan structure, which would impact on the plaque formation via augmentation of the susceptibility to other bacterial components. The finding suggests that some bacterial components will gain the ability to attach with other factors when they encountered specific antibodies and thus, the magnitude of susceptibility of orally administrated H. pylori to gastric mucosa may be augmented in the presence of S3 MAb in vivo.

Very recently, Akhiani et al. reported that H. pylori-specific antibodies are not only dispensable for protection against bacterial infection, but are rather detrimental to the elimination of the bacteria and appear to impair the gastric inflammatory responses (2). We have also noticed that the magnitude of H. pylori urease-specific IgG, but not IgA, had a positive correlation with the progression of chronic gastritis (12). Our present results clearly show that there is an IgG antibody specific for H. pylori urease that augments their colonization in vivo and suggest a new strategy to stop the disease progression by H. pylori via driving the immune responses against H. pylori from humoral to cellular way.

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