Metallothionein is a crucial protective factor against Helicobacter pylori-induced gastric erosive lesions in a mouse model

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Metallothionein (MT) is a low-molecular-weight, cysteine-rich protein that can act not only as a metal-binding protein, but also as a ROS scavenger. In the present study, we examined the role of MT in the protection against H. pylori-induced gastric injury using MT-null mice. Female MT-null and wild-type mice were challenged with H. pylori SS1 strain, and then histological changes were evaluated with the updated Sydney grading system at 17 and 21 wk after challenge. Although the colonization efficiency of H. pylori was essentially the same for MT-null and wild-type mice, the scores of activity of inflammatory cells were significantly higher in MT-null mice than in wild-type mice at 17 wk after challenge. Histopathological examination revealed erosive lesions accompanied by infiltration of inflammatory cells in the infected MT-null mice but not in wild-type mice. Furthermore, activation of NF-κB and expression of NF-κB-mediated chemokines such as macrophage inflammatory protein-1α and monocytes chemoattractant protein-1 in gastric cells were markedly higher in MT-null mice than in wild-type mice. These results suggest that MT in the gastric mucosa might play an important role in the protection against H. pylori-induced gastric ulceration.

gastric ulcer; reactive oxygen species; NF-κB; chemokine

Helicobacter pylori (H. pylori) infection is a potential factor leading to gastritis in humans. The infection is not cleared by gastric immune responses and, after a prolonged period of infection, much more severe clinical symptoms such as peptic ulcers, carcinoma, and lymphoma may develop (43). It is well established that H. pylori infection stimulates the generation of reactive oxygen species (ROS) via inflammatory cell responses (20, 26). However, the pathogenesis of H. pylori-associated gastric disease has not been fully elucidated. Animal models of H. pylori infection using cats, dogs, piglets, or ferrets have to date shown variable and, in some instances, poor colonization efficiency of H. pylori (12, 16, 25, 37, 44). In 1997, after screening a variety of fresh clinical isolates obtained from patients as well as long-term adaptation in mice, Lee et al. (18, 31) isolated a strain of H. pylori with very good colonizing ability in C57BL/6 mice and named it the Sydney strain of H. pylori (SS1 strain). Several studies have shown that SS1 strain induces robust gastritis as indicated by polymorphonuclear cell (PMN) infiltration (18, 25, 27). However, severe gastric ulceration or erosion has not been observed in SS1 H. pylori-infected mice (27).

Metallothionein (MT) is a low-molecular-weight, cysteine-rich, metal-binding protein. Of the four isoforms of MT in mice, MT-I and MT-II are deficient, exhibit increased sensitivity to many agents including metals, hormones, cytokines, and alkylating agents (2, 4, 7, 17, 18, 32). MT-I and MT-II have been reported that MT-null mice are more sensitive to lipopolysaccharide (LPS)/D-galactosamine-induced lethality and that the levels of macrophage inflammatory protein (MIP)-1α and monocytes chemoattractant protein (MCP)-1 in the lung were greater in MT-null mice than in wild-type mice after LPS treatment (13, 16). Furthermore, we have shown that MT plays a protective role in gastroduodenal mucosal injury caused by ethanol ingestion (40).

In vitro studies have revealed that infection with H. pylori induces the expression of chemokines by the activation of NF-κB in mucosal epithelial cells and then facilitates inflammatory responses (3, 10, 14). On the other hand, we have reported that MT deficiency affects redox status, activating...
NF-κB-dependent gene expression (32). MT may play a role in modulating the inflammatory responses to *H. pylori* infection and the associated gastritis by the sequestration of ROS and the suppression of NF-κB-dependent gene expression. In the present study, we infected MT-null mice with the *H. pylori* SS1 strain to examine the role of gastric MT in the protection against *H. pylori* and found that the SS1 strain induced gastric erosive lesions with infiltration of leukocytes in MT-null mice. This is the first report that *H. pylori* SS1 induces erosive lesions in a mouse model, which may promote the elucidation of pathogenesis of human *H. pylori*-associated gastritis.

**MATERIALS AND METHODS**

*Animals.* MT-I- and MT-II-deficient mice and the corresponding wild-type control mice were kindly provided by Dr. Choo (Murdoch Institute for Research into Birth Defects, Royal Children’s Hospital, Parkville, Australia), and maintained at the National Institute for Environmental Studies (Tsukuba, Japan). These mice were originally developed on a mixed genetic background of OLA129 and C57BL/6 strains. Since C57BL/6 mice have shown the most efficient colonization and the most severe gastritis following infection with *H. pylori* SS1 strain (31), we first backcrossed these mice with C57BL/6 Jcl (CLEA Japan, Tokyo, Japan) for ten generations to replace 99.9% of their genome with that of C57BL/6 Jcl. Furthermore, as spontaneous infection with *Helicobacter* was detected in both MT-null and wild-type mice, we performed embryo transfer for the eradication of microorganism infection. After the embryo transfer, we confirmed that no microorganism was detected in the stomach of adult mice. The animals were maintained at the Laboratory Animal Research Center of Kitasato University, housed in polycarbonate cages with a 12 h:12 h light-dark cycle, 55 ± 5% humidity, and an ambient temperature of 22 ± 1°C and had access to food and water ad libitum. Animal protocols were approved by the Kitasato University School of Pharmaceutical Sciences Animal Use and Care Committee.

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**Fig. 1.** Metallothionein (MT) expression in the gastric tissue sections from infected and uninfected mice. MT was immunohistochemically detected in the stomach of uninfected wild-type mice (*A*), infected wild-type mice at 21 wk postinfection (*B*), uninfected MT-null mice (*C*), and infected MT-null at 21 wk postinfection (*D*). Original magnifications: (*A–D*) ×200.
and all experiments were conducted in accordance with the Institute for Laboratory Animal Research (ILAR) Guide for Care and Use of Laboratory Animals. Seven-week-old female mice were used for experiments.

**Bacteria and culture conditions.** The SS1 strain of *H. pylori* was obtained from Dr. Toshifumi Hibi (Keio University, Tokyo, Japan). Frozen SS1 in a brain-heart infusion broth (Eiken Chemical, Tokyo, Japan) containing 15% (vol/vol) fetal bovine serum (FBS) and 15% (vol/vol) glycerol was thawed and then streaked on Pourmedia HP selective agar plates (Eiken Chemical). The plates were incubated in an anaerobic jar (Oxoid, Basingstoke, UK) with a microaerophilic gas-generating kit (Oxoid) at 37°C for 5 days. After incubation, the bacteria were resuspended in 1 ml of PBS and then incubated in 50 ml of the brain-heart infusion broth containing 5% (vol/vol) FBS for 5 days with shaking. Ten milliliters of glycerol and 10 ml of FBS were added to the incubated broth to prepare stock cultures, and the stock cultures were then stored at −80°C until challenge.

**H. pylori infection.** For *H. pylori* challenge, 1.8 ml of the stock culture solution was added to 50 ml of the brain-heart infusion broth containing 10% (vol/vol) FBS and then incubated in an anaerobic jar with a microaerophilic gas-generating kit at 37°C for 48 h with shaking. Approximately 1 × 10^10 colony-forming units (CFUs)/ml of bacterial suspension in a volume of 0.5 ml were given orally using a stainless steel catheter. Mice were challenged three times over a 6-day period. Uninfected control mice received the brain-heart infusion broth only. At 17 and 21 wk after challenge, from each group, 10 mice were euthanized for the examination of colonization efficiency and another 10 mice for the histopathological and biochemical examination.

**Evaluation of *H. pylori* infection.** *H. pylori* infection was evaluated by counting the colonies following microaerobic bacterial culture. The PCR primers for the *VacA*, *CagA*, and *VacAs2* genes were 5'-/H11032-ATGGAAATACAAACACAC-3' (Forward, Fw) and 5'-/H11032-CATAACTAGCGCCTTGCAC-3' (Reverse, Rv), respectively. A PCR assay was carried out with synthesized primers for MIP-1α (sense: 5'-TTTGATGACACTAACCATGAAAGGCTTCCACACCA-3' and antisense: 5'-AAAGGATCTCCAGGACATTGAGG-3') and MCP-1 (sense: 5'-CTTTGCTTGAATGTGAAGTTGACC-3' and antisense: 5'-CTCAAACACAAAGTTAAACC-3'). The reaction mixture contained the forward and reverse primers (0.1 μM each), dNTP (0.25 mM), 20 mM Tris-HCl (pH 8.0), 100 mM KCl, 0.5 mM MgCl₂, 0.05% of Taq DNA polymerase (Takara Bio, Shiga, Japan), and 0.4 μl of cDNA in a total reaction volume of 20 μl. As a control, 0.4 μl of cDNA was amplified by using primers for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (sense: 5'-ACCACACACTGGCTTAC-3' and antisense: 5'-TCCAGGGTACCAATGGGC-3').

**Electrophoretic mobility shift assay.** Gastric mucosa was scraped from the stomach with a glass coverslip and was homogenized. Nuclear extracts were prepared from the tissue homogenate as described previously (32) and incubated with 32P-labeled 22-mer double-strand NF-κB oligonucleotide (5'-AGTTGAGGGGGACTTTTCCAGGC-3') for 30 min at room temperature. Native 4% polyacrylamide gels were used to analyze the samples. A double-stranded mutated oligonucleotide (5'-AGTTGAGGATcAegagaCAGGGC-3', with mutated nucleotides shown in small letters) was used to examine the specificity of binding. The radioactive bands in dried gels were visualized and quantified with the use of a Fuji Bio-Imaging analyzer (LAS3000; Fuji Photo Film, Tokyo, Japan).

**Reverse transcriptase (RT)-PCR.** Total RNA was isolated from the gastric mucosa using an RNeasy Fibrous Tissue Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer’s instructions. The yield and purity of RNA were quantified by measuring the ratio of optical density at 260 and 280 nm. Five micrograms of total RNA was reverse transcribed to cDNA using SuperScript II (Invitrogen Life Technologies, Merelbeke, Belgium) according to the supplier’s instructions. PCR reactions were carried out with synthesized primers for MIP-1α and MCP-1 and 32P-labeled 22-mer double-strand oligonucleotides. The reaction mixture was denatured in a water bath at 95°C for 5 min and cooled on ice. Reverse transcription and PCR were carried out with synthesized primers and 0.4 μl of cDNA in a total reaction volume of 20 μl. As a control, 0.4 μl of cDNA was amplified by using primers for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (sense: 5'-ACCACACACTGGCTTAC-3' and antisense: 5'-TCCAGGGTACCAATGGGC-3').

**Histological evaluation.** Whole or a half of the stomach was fixed in 10% neutral buffered formalin, embedded in paraffin, and cut into 3-μm sections, stained with hematoxylin-eosin, and histopathologically examined by the same histopathologist who was unaware of the other findings. Gastric mucosal alterations were classified according to the updated Sydney grading system. Scores of PMN activity and chronic inflammation were graded with respect to the density of the PMN and mononuclear cells infiltrate, respectively, as follows: 0 = no infiltration (same degree as in uninfected mice), 1 = mild, 2 = moderate, and 3 = severe. Hyperplasia score was graded as follows: 0 = nonhyperplasia (same degree as in uninfected mice), 1 = mild, 2 = moderate, and 3 = severe.
and antisense 5'-ATCAGCACAGCTTTCC-3'). After initial denaturation (4 min, 95°C), 29 (for MIP-1α), 35 (for MCP-1), and 30 (for GAPDH) amplification cycles were performed by using a thermal cycler (Bio-Rad, Hercules, CA). One cycle consisted of denaturation at 94°C for 30 s, annealing at 64°C (for MIP-1α), 56°C (for MCP-1), or 60°C (for GAPDH) for 30 s and extension at 74°C for 30 s. After the last cycle, final extension at 72°C for 4 min was carried out. PCR products (138 bp for GAPDH, 294 bp for MIP-1α, and 307 bp for MCP-1) were identified by electrophoresis on a 2% agarose gel containing ethidium bromide.

Statistical analysis. Results are expressed as means ± SE. Assessment of differences among means was carried out with Mann-Whit-
RESULTS

MT expression in the gastric tissue section. Immunohistochemical examination of MT expression in wild-type and MT-null mice was shown in Fig. 1. Intense staining of MT was observed in chief cells of the gastric pit mucosa in nontreated wild-type mice (Fig. 1A) as well as in H. pylori-infected wild-type mice (Fig. 1B). There was no positive staining of MT in the stomach of MT-null mice regardless of H. pylori infection (Fig. 1, C and D).

H. pylori SS1 infection of MT-null and wild-type mice. At 17 and 21 wk after challenge with H. pylori SS1 strain, CFUs of H. pylori were determined by microaerobic cultivation. Large numbers of transparent and colorless colonies, characteristic of H. pylori, were detected on agar plates. There was no difference in the levels of bacterial colonization between MT-null and wild-type mice at either 17 or 21 wk (Fig. 2). CFUs of H. pylori were not detected in noninfected MT-null or wild-type mice. PCR analyses revealed expression of CagA, VacA, and VacAs2 genes but not babA2 gene in the colonies isolated from the stomach of both MT-null and wild-type mice (data not shown), indicating that the detected Helicobacter colonies are definitely derived from the H. pylori SS1 strain.

Macroscopic evaluation: severe erosion in the stomach of MT-null mice. Figure 3 shows representative macroscopic findings of the stomach. No remarkable change was observed in the gastric mucosa of uninfected control mice (Fig. 3A). At 17 wk after challenge, mild hypertrophy was observed in the gastric mucosa in all wild-type mice, but no erosion was detected (Fig. 3B). All MT-null mice showed hypertrophy in the gastric mucosa. Furthermore, erosive lesions with bleeding were found at the antro-oxynitic transitional zone in four of the 10 infected MT-null mice (Fig. 3C). These erosive lesions were characterized by the punched-out shape and sharply defined margins that were firm and thickened (Fig. 3D). However, these lesions did not invade muscularis mucosa.

At 21 wk after challenge, the infected wild-type mice exhibited more severe hypertrophy in the gastric mucosa than those at 17 wk, but no erosion was observed (Fig. 3E). On the other hand, four of the 10 infected MT-null mice showed...
erosive lesions in the gastric mucosa although the erosive lesions were much shallower and smaller than those at 17 wk after challenge (Fig. 3, F and G).

Microscopic evaluation: ulceration accompanied by remarkable infiltration of inflammatory cells in the stomach of MT-null mice. In the uninfected control mice, the gastric mucosa had an intact epithelial layer and glandular cells with continuous gastric pits (Fig. 4A). In the wild-type mice infected with *H. pylori* at 17 wk after challenge, the epithelial layer of gastric mucosa was intact, but mild infiltration of PMN, lymphocytes, and macrophages was observed (Fig. 4B). In the infected MT-null mice, the lamina propria mucosae was disrupted by the infiltration of inflammatory cells and the nuclei of mucosal epithelial cells near the erosive lesion site were enlarged (Fig. 4C). As shown in Table 1, scores of both PMN activity and chronic inflammation in the infected MT-null mice were about twofold higher than those in the infected wild-type mice at 17 wk after challenge, suggesting that the deficiency of MT gene expression accelerates accumulation of PMN and mononuclear cells toward inflammatory sites.

At 21 wk after challenge, mild infiltration of PMN and mononuclear leukocytes was observed in the submucosa as well as the mucosa of the stomach in all infected mice (Fig. 4E). During the period between 17 and 21 wk after challenge, in the infected MT-null mice, scores of PMN activity were decreased by about 50%, but those for chronic inflammation remained unchanged. On the other hand, in the wild-type mice, both scores tended to increase during this period. As a result, scores of PMN activity and chronic inflammation were not significantly different between MT-null and wild-type mice at 21 wk after challenge (Table 1). Furthermore, hyperplasia in the lamina propria mucosae and submucosa was observed in both mice strains. These findings suggest the restoration from severe inflammatory reaction, which is also reported in other models of stomach lesions (18, 44).

Enhancement of MIP-1α and MCP-1 expression and NF-κB DNA-binding activity in the stomach of MT-null mice. During inflammatory reactions, chemokines such as MIP-1α and MCP-1 induce accumulation of neutrophiles, lymphocytes, and macrophages at inflamed sites (1, 45). As elevated levels of MIP-1α and MCP-1 were observed in *H. pylori*-associated gastritis (14), we next examined the mRNA levels of these chemokines. As shown in Fig. 5A, both mRNA levels of MIP-1α and MCP-1 in the stomach of the infected MT-null mice were markedly higher than those of wild-type mice. Activation of transcription factor NF-κB is involved in the expression of MIP-1α and MCP-1 (1, 9), and we have previously reported that deficiency of MT gene expression activates NF-κB-dependent gene expression through the enhancement of IkB degradation (32). Thus we examined the binding activity of nuclear NF-κB to DNA in the gastric mucosa of MT-null and wild-type mice by EMSA. As shown in Fig. 5B, the DNA-binding activity of nuclear protein prepared from the stomach of *H. pylori*-infected MT-null mice was higher than that of the infected wild-type mice. Specificity of the binding was confirmed by the observation that this binding competed with unlabeled wild-type probe but not with the probe having a mutated NF-κB-binding site (Fig. 5B). These results suggest that the deficiency of MT expression enhances NF-κB activity, leading to increased expressions of MIP-1α and MCP-1 in the gastric cells of *H. pylori*-infected mice.

**DISCUSSION**

In the present study, we infected the *H. pylori* SS1 strain to examine the role of gastric MT in the protection against *H. pylori* and found that MT-null mice were more sensitive to *H. pylori* than wild-type mice. Furthermore, we found that the SS1 strain induced gastric erosive lesions with infiltration of leukocytes in some of the MT-null female mice. This is the first

![Fig. 5.](http://ajpgi.physiology.org/)
report to demonstrate that \textit{H. pylori} SS1 induces erosive lesions in a mouse model.

Previous studies (18, 27, 31, 39) have shown that susceptibility to \textit{Helicobacter} is strongly influenced by mouse strain. Among many inbred strains of mice, C57BL/6 mice appear to be the most sensitive strain to \textit{Helicobacter} infection (31). Several groups have demonstrated that C57BL/6 mice showed vigorous Th1-mediated gastric inflammation after infection with \textit{Helicobacter}, whereas BALB/c mice showed minimal gastric inflammation (27, 39). In general, there is an inverse relationship between the strength of Th1 response and the degree of \textit{Helicobacter} colonization. We succeeded here in inducing gastric erosive lesions in MT-null mice by infection with the \textit{H. pylori} SS1 strain. Although the original MT-null mice had mixed genetic background of OLA129 and C57BL/6, the backcrossing of MT-null and the corresponding wild-type mice toward C57BL/6J for 10 generations might have permitted the efficient colonization of \textit{H. pylori} in the present study.

Although Tran et al. (42) reported the effect of \textit{H. pylori} SS1 infection in MT-null mice, they did not find remarkable gastritis accompanying erosive lesions but only the formation of functional atrophy. In addition, they reported that \textit{H. pylori} infection was greater in MT-null mice, but gastritis scores of the stomach were the same for MT-null and wild-type mice at 4, 8, and 16 wk after challenge with \textit{H. pylori}. Probably, the discrepancy between Tran et al.’s study and ours might result from the difference in the numbers of \textit{H. pylori} inoculation (10^8 CFUs in Tran et al.’s study vs. 5 \times 10^7 CFUs in our study) or in the number of generation of backcrossing toward C57BL/6 mice (3 in Tran et al.’s study vs. 10 in ours).

MT plays an important role in the detoxification of heavy metals via its high sulphhydril content (2, 4, 15, 17, 33). Recent studies have further indicated that MT is involved in the protection against tissue damage, including gastric damage, caused by a wide range of stressors. Miura et al. (24) reported that gastric ulceration induced by administration of HCl-ethanol was suppressed by intravenous injection of purified MT-II. We also demonstrated that ethanol-induced gastric-duodenal mucosal lesions in MT-null mice were more severe than those in wild-type mice (40). On the other hand, Mannick et al. (22) reported that the levels of MT-I mRNA in biopsy samples from the gastric antral of \textit{H. pylori}-infected patients were lower than those from uninfected patients. These results suggest that MT is an important protective factor in the stomach.

It has been indicated that MT functions as a cytoprotective factor via its ability to scavenge ROS, which is involved in a variety of tissue damage including paraquat and ultraviolet (34, 36). ROS production is also involved in ethanol-induced gastric damage, which is protected by MT induction (40). \textit{H. pylori}-induced gastritis and peptic ulcer are associated with increased production of ROS in the gastric mucosa (20, 26, 29). The ROS produced at inflamed sites affects the activity of several transcription factors including NF-\(\kappa\)B, which regulates the expression of inflammatory cytokines such as interleukin (IL)-1 and IL-6 and chemokines such as IL-8, MIP-1\(\alpha\), RANTES, and MCP-1 (1, 9). NF-\(\kappa\)B activity is repressed in resting cells by being anchored in the cytoplasm by tightly bound inhibitory protein I\(\kappa\)B. Activators of NF-\(\kappa\)B such as IL-1 and LPS induce phosphorylation and subsequent degradation of I\(\kappa\)B and allow NF-\(\kappa\)B to translocate into the nucleus. Degradation of I\(\kappa\)B is regulated by ROS in the cytoplasm. In a previous study (32), we showed that MT regulates the degradation of I\(\kappa\)B and subsequent activation of NF-\(\kappa\)B via its ability to scavenge ROS. \textit{H. pylori} infection leads to activation of NF-\(\kappa\)B and increased NF-\(\kappa\)B-dependent gene expression in cultured cell lines. For example, \textit{H. pylori} SS1 can induce the expression of IL-6 and IL-8 by Toll-like receptor (TLR)-2-mediated NF-\(\kappa\)B activation in epithelial cells (11, 41). The LPS prepared from \textit{H. pylori} can induce the expression of IL-1, IL-6, and IL-8 by TLR-2- or TLR-5-mediated NF-\(\kappa\)B activation (5, 38). However, the amount of these cytokines produced in response to \textit{H. pylori} is one-hundredth that produced in response to the LPS prepared from \textit{Escherichia coli} or \textit{Salmonella enterica} (21). Consistent with these reports, we found that \textit{H. pylori}-induced activity of NF-\(\kappa\)B in gastric mucosa of wild-type mice was very weak. On the other hand, strong NF-\(\kappa\)B activity was induced by \textit{H. pylori} SS1 challenge in the gastric mucosa cells of MT-null mice (Fig. 4B). Reflecting the higher activation of NF-\(\kappa\)B in MT-null mice, mRNA levels of MIP-1\(\alpha\) and MCP-1 in the stomach cells were higher in \textit{H. pylori}-infected MT-null mice than in wild-type mice (Fig. 4A). In wild-type mice, NF-\(\kappa\)B activity and chemokine levels might be depressed by MT to levels at which severe inflammation cannot occur even when challenged with \textit{H. pylori}.

MT expression was observed in gastric mucosa in nontreated wild-type mice as well as in \textit{H. pylori}-infected wild-type mice (Fig. 1). Although our immunohistochemical analysis could not show significant difference in MT levels between nontreated and infected mice, Mitani et al. (23) recently reported that MT expression in human gastric mucosa was higher in \textit{H. pylori}-negative patients than in positive patients. Reduction of MT levels might be associated with \textit{H. pylori} infection. On the contrary, MT expression was not observed in the inflammatory lesions with hyperplastic growth of the glandular epithelial cells at 21 wk postinfection (Fig. 1). These findings suggest that MT may not be involved in the process of regeneration of gastric mucosa that was destroyed by \textit{H. pylori} infection. Chronological examination of MT expression at the site of affected lesions may be useful for the better understanding of the precise roles of MT in the \textit{H. pylori} infection.

In conclusion, MT might play an important role in gastric cytoprotection against \textit{H. pylori} infection, presumably by scavenging ROS and thereby inhibiting the NF-\(\kappa\)B-mediated induction of inflammatory chemokines. MT induction may have a therapeutic efficacy in the prevention of \textit{H. pylori}-induced gastric ulceration and, consequently, carcinogenesis.

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