**Helicobacter pylori** Lipopolysaccharide Binds to CD14 and Stimulates Release of Interleukin-8, Epithelial Neutrophil-Activating Peptide 78, and Monocyte Chemotactic Protein 1 by Human Monocytes

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**Helicobacter pylori** gastritis is characterized by leukocyte infiltration of the gastric mucosa. The aims of this study were to determine whether *H. pylori*-derived factors stimulate chemokine release from human monocytes and to ascertain whether *H. pylori* lipopolysaccharide (LPS) may be responsible for this effect. Human peripheral blood monocytes were exposed to an *H. pylori* water extract (HPE) or to purified *H. pylori* LPS. Levels of the chemokines interleukin-8 (IL-8), epithelial neutrophil-activating peptide 78 (ENA-78), and monocyte chemotactic protein 1 (MCP-1) were measured by enzyme-linked immunosorbent assay. The contribution of *H. pylori* LPS to monocyte activation was determined by using the LPS antagonist *Rhodobacter sphaeroides* lipid A (RSLA) and a blocking monoclonal antibody to CD14 (60bca). HPE increased monocyte secretion of IL-8, ENA-78, and MCP-1. Heat treatment of HPE did not reduce its ability to activate monocytes. Purified *H. pylori* LPS also stimulated monocyte chemokine production but was 1,000-fold less potent than *Salmonella minnesota* lipid A. RSLA blocked *H. pylori* LPS-induced monocyte IL-8 release in a dose-dependent fashion (maximal inhibition 82%, *P* < 0.001). RSLA also inhibited HPE-induced IL-8 release (by 93%, *P* < 0.001). The anti-CD14 monoclonal antibody 60bca substantially inhibited IL-8 release from HPE-stimulated monocytes (by 88%, *P* < 0.01), whereas the nonblocking anti-CD14 monoclonal antibody did not. These experiments with potent and specific LPS inhibitors indicate that the main monocyte-stimulating factor in HPE is LPS. *H. pylori* LPS, acting through CD14, stimulates human monocytes to release the neutrophil-activating chemokines IL-8 and ENA-78 and the monocyte-activating chemokine MCP-1. Despite its low relative potency, *H. pylori* LPS may play an important role in the pathogenesis of *H. pylori* gastritis.

*Helicobacter pylori* is estimated to infect over one-half of the world’s population (4). Although most infections are asymptomatic, *H. pylori* is associated with the development of gastric and duodenal ulcers, gastric carcinoma, and gastric lymphoma (2–4, 10). All individuals with *H. pylori* infection have gastritis, usually involving the antrum, that is characterized by inflammatory cell infiltration with polymorphonuclear cell invasion of the gastric lamina propria and glandular epithelium (10, 11, 20).

The pathophysiologic mechanisms leading to neutrophil infiltration in *H. pylori* gastritis have been the subject of intense investigation (11, 20, 27). *H. pylori* is minimally invasive; for this reason most investigators have focused on soluble factors, of either host or bacterial origin, which may mediate neutrophil recruitment. Host factors include proinflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor (TNF), and IL-8, all of which are increased in the antral mucosa of individuals with *H. pylori* gastritis (15, 21, 23, 40).

Chemokines are a superfamily of closely related chemoattractant cytokines which specialize in mobilizing leukocytes to areas of immune challenge (7, 8, 49). These inductive proinflammatory peptides potently stimulate leukocyte migration along a chemotactic gradient. They also modulate leukocyte adhesion molecule expression and other leukocyte functions that are necessary for leukocytes to leave the circulation and infiltrate tissues. Thus, increased chemokine production and release is an important mechanism for leukocyte recruitment in response to injury or infection. Chemokines are divided into groups or families that are defined by characteristic cysteine motifs. Four families of chemokines—C-X-C, C-C, C, and C-X3-C—have now been described, where C is a conserved cysteine residue and X is any other amino acid (7, 8, 49). IL-8 and epithelial neutrophil-activating peptide 78 (ENA-78) are C-X-C chemokines; both activate neutrophils, and both carry a common ELR (Glu-Leu-Arg) amino acid motif immediately adjacent to their C-X-C sites (8). Monocyte chemotactic protein 1 (MCP-1) is a C-C chemokine that stimulates mononuclear leukocytes.

IL-8 levels are increased in *H. pylori* gastritis, and a number of studies have demonstrated transcriptional upregulation of IL-8 production by *H. pylori*-infected gastric epithelial cells (13–15, 17, 21, 23, 37, 40, 48). Monocytes and macrophages are another major source of IL-8 production, and the present study focuses on the ability of water-soluble factor release by *H. pylori* to activate the production of IL-8 and other chemokines by human monocytes. Monocytes are also an important source of IL-1 and TNF, which activate endothelial-cell adhesion molecule expression and thereby cooperate with chemokines such as IL-8 in regulating neutrophil diapedesis (25, 41).
A number of soluble factors released by *H. pylori*, including urease and lipopolysaccharide (LPS), activate phagocytic leukocytes (11, 16, 31–33, 35). *H. pylori* LPS is a monocyte chemotactant and mitogen; it activates monocytes to release reactive oxygen intermediate superoxide anion and upregulates monocyte production of IL-1, TNF, and IL-6 (6, 9, 29, 32, 38, 42). Its effects on neutrophils are less dramatic, but it does prime them to respond to other stimuli (39). Despite this wide range of activity, *H. pylori* LPS is of low potency compared to the LPS produced by gram-negative bacteria of the *Enterobacteriaceae* family, such as *Escherichia coli* or *Salmonella* species (9, 18, 19, 34–36, 38, 39, 42). This has led to the hypothesis that *H. pylori* has evolved to produce a less-inflammatory LPS to prime them to respond to other stimuli (39). Despite this wide range of activity, *H. pylori* LPS is of low potency compared to the LPS produced by gram-negative bacteria of the *Enterobacteriaceae* family, such as *Escherichia coli* or *Salmonella* species (9, 18, 19, 34–36, 38, 39, 42). This has led to the hypothesis that *H. pylori* has evolved to produce a less-inflammatory LPS to prime them to respond to other stimuli (39).

The goals of this study were (i) to determine whether water-soluble factors released by *H. pylori* could activate the release of chemokines, including IL-8, from human monocytes; (ii) to determine whether *H. pylori* water-soluble factors could up-regulate adhesion molecule expression by human endothelial cells; and (iii) to determine the contribution of *H. pylori* LPS to monocyte and/or endothelial cell activation. To address the first goal, we examined the release of the neutrophil-activating, C-X-C chemokines IL-8 and ENA-78 and the monocyte-activating C-C chemokine MCP-1 from isolated human peripheral blood monocytes exposed to *H. pylori* water extract. To address the second goal, we examined the surface expression of the leukocyte adhesion receptor ICAM-1 (intracellular adhesion molecule 1) by human endothelial cells after exposure to the same *H. pylori* water extract. To address the final goal, we used the potent and specific LPS antagonist *Rhodobacter sphaeroides* lipid A, as well as monoclonal antibodies directed against the CD14 LPS receptor. We found that *H. pylori* water extract activates chemokine release from monocytes but does not up-regulate ICAM-1 expression in endothelial cells. Furthermore, our results indicate that, despite its low relative potency, LPS is the main water-soluble *H. pylori* factor activating monocyte chemokine release in vitro.

**MATERIALS AND METHODS**

*H. pylori* preparations. *H. pylori* 43504 (American Type Culture Collection, Manassas, Va.) was plated on *Campylobacter* agar with Skirrow’s supplements (Diffco, Detroit, Mich.) and incubated at *80°C*. *H. pylori* cells, constitutively present in water (Baxter, Deerfield, Ill.), supplemented with 10% defibrinated sheep blood (BBL; Becton Dickinson (Difco, Detroit, Mich.), reconstituted in pyrogen-free water (Baxter, Deerfield, Manassas, Va.) was plated on *H. pylori* immunosorbent assay (ELISA) (23, 24, 26). For the IL-8 ELISA, the wells of an Immulon II, 96-well microtiter plate (Dynatech, Chantilly, Va.) were coated with goat anti-human IL-8 antibody (R & D Systems, Minneapolis, Minn.), at 5 µg/ml in 100 µl of carbonate coating buffer (35 mM NaHCO₃, 15 mM Na₂CO₃, [pH 9.6]) and incubated overnight at 4°C. The wells were washed with PBS containing 0.05% Tween 20 (pH 7.0) (PBS-Tween) between each incubation step. Wells were blocked with 2% bovine serum albumin (Sigma, St. Louis, Mo.) in PBS-Tween for 1 h at 37°C. After being washed, samples and IL-8 standards (R&D Systems) in 100 µl of R10 medium (RPMI 1640; Cellerio) were added. After 2 h, wells were incubated at 37°C for 1 h. Biotin-labeled anti-IL-8, at 2 µg/ml in 100 µl of 2% bovine serum albumin-PBS-Tween, was then added to the wells, and the wells were incubated at 37°C for 1 h. The anti-IL-8 was biotin-labeled by using NHS-LC biotin (Pierce, Rockford, Ill.) according to the manufacturer’s instructions. After being washed with PBS containing 0.05% Tween 20, 100 µl of tetramethylbenzidine substrate solution (Kirkegaard & Perry Laboratories, Inc., Gaithersburg, Md.) was added to each well, and the reaction was stopped after 5 min with 50 µl of 3 M H₂SO₄. The IL-8 ELISA was determined with an automated microlate photometer (Dynatech), and the concentrations of IL-8 were determined by comparison with the IL-8 standard curve. The IL-8 ELISA showed no cross-reactivity with a panel of other cytokines and chemokines and had a sensitivity of <50 pg of IL-8.

The ENA-78 and MCP-1 assays followed a method similar to that used for the IL-8 ELISA except that Maxisorb plates (Nunc, Naperville, Ill.) were used. For the ENA-78 ELISA, plates were coated with goat anti-ENA-78 (R&D Systems), and biotin-labeled goat anti-ENA-78 was used as the secondary antibody. For the MCP-1 ELISA, plates were coated with goat anti-MCP-1 (R&D Systems) and biotin-MCP-1 (Genzyme, Cambridge, Mass.) was used as the secondary antibody, followed by biotinylated donkey anti-rabbit immunoglobulin G (IgG) (1:10,000; Amersham). Human recombinant ENA-78 and MCP-1 were used as standards (R&D Systems). Both assays showed a sensitivity of ~50 pg/ml.

**Chemokine assays.** Chemokine release in vitro. To address the final goal, we used the potent and specific LPS antagonist *Rhodobacter sphaeroides* lipid A, as well as monoclonal antibodies directed against the CD14 LPS receptor. We found that *H. pylori* water extract activates chemokine release from monocytes but does not up-regulate ICAM-1 expression in endothelial cells. Furthermore, our results indicate that, despite its low relative potency, LPS is the main water-soluble *H. pylori* factor activating monocyte chemokine release in vitro.

**Cell-ELISA for ICAM-1 expression by human endothelial cells.** Early-passage human endothelial cells (Endo-Pack-UV; Clonetics, San Diego, Calif.) were grown to confluence on 96-well tissue culture plates. Endothelial monolayers were incubated with R10 medium (control), IL-1β (positive control), *H. pylori* LPS, HPE, or monocyte conditioned media. After overnight incubation the endothelial monolayers were fixed with 1% formaldehyde, permeabilized with 0.05% Tween 20 (pH 7.0) between each incubation step. Wells were incubated at 37°C for 1 h. Biotin-labeled anti-IL-8, at 2 µg/ml in 100 µl of 2% bovine serum albumin-PBS-Tween, was then added to the wells, and the wells were incubated at 37°C for 1 h. Biotin-labeled anti-IL-8, at 2 µg/ml in 100 µl of 2% bovine serum albumin-PBS-Tween, was then added to the wells, and the wells were incubated at 37°C for 1 h. Anti-IL-8 was biotin-labeled by using NHS-LC biotin (Pierce, Rockford, Ill.) according to the manufacturer’s instructions. After being washed with PBS containing 0.05% Tween 20, 100 µl of tetramethylbenzidine substrate solution (Kirkegaard & Perry Laboratories, Inc., Gaithersburg, Md.) was added to each well, and the reaction was stopped after 5 min with 50 µl of 3 M H₂SO₄. The IL-8 ELISA was determined with an automated microlate photometer (Dynatech), and the concentrations of IL-8 were determined by comparison with the IL-8 standard curve. The IL-8 ELISA showed no cross-reactivity with a panel of other cytokines and chemokines and had a sensitivity of <50 pg of IL-8.

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**Inhibition of LPS effects by using *R. sphaeroides* lipid A and anti-CDI4.** In some experiments the LPS antagonist B287 (Eisai Institute, Andover, Mass.) was added prior to monocyte stimulation (22, 47). B287 is a synthetic compound whose structure is identical to the proposed structure of *R. sphaeroides* lipid A (RSLA) (12, 22, 47). In other experiments a blocking anti-CD14 monoclonal antibody, 60bca (10 µg/ml), was added prior to the addition of stimuli (51). A monoclonal antibody, 26C (10 µg/ml), which recognizes CD14 but does not block LPS binding to CD14, was used as a control. These anti-CD14 monoclonal antibodies were prepared from a human monoclonal cell line (CD14, 26C) by John Schreiber, Rainbow Babies Children's Hospital, Cleveland, Ohio. Medium supplemented with 2% human serum was used for all of the experiments with the anti-CD14 antibodies since fetal calf serum contains substantial amounts of soluble CD14. Monocytes were incubated with each of the different stimuli at 37°C for 6 h unless otherwise specified. The monoclonal conditioned media were then harvested, and cytokine levels were measured by ELISA.

**Statistical analyses.** Statistical analyses were performed by using SigmaStat for Windows version 2.0 (Jandel Scientific Software, San Rafael, Calif.). Unless stated otherwise, analysis of variance followed by protected *t*-tests was used for the intergroup comparisons. A *P* value of <0.05 was considered statistically significant.
RESULTS

HPE stimulates chemokine release from human monocytes. HPE, which contains water-soluble factors released from *H. pylori*, activated the release of the chemotactic cytokines IL-8, MCP-1, and ENA-78 from human monocytes. Stimulation of IL-8 release from monocytes by HPE was dose dependent (Fig. 1). Significant monocyte stimulation was evident with concentrations of HPE of 0.06% or greater. In time course experiments, monocytes exposed to 1% HPE showed a marked increase in IL-8 release within 2 h compared to control monocytes, and increased IL-8 release was sustained for at least 24 h (data not shown). HPE also caused a dose-dependent increase in the production of the chemokines MCP-1 (Fig. 2) and ENA-78 (data not shown) by human monocytes.

*H. pylori* LPS stimulates chemokine release from human monocytes. Purified *H. pylori* LPS at concentrations of 10 ng/ml or greater caused a significant increase in chemokine release from human monocytes (Fig. 3 and 4). *S. minnesota* lipid A also caused a dose-dependent increase in chemokine production. As shown in Fig. 4, the maximal levels of IL-8 produced after stimulation of monocytes with *H. pylori* LPS or lipid A were similar. However, as previously reported (9, 18, 19, 34, 36, 38, 39, 42), there was a marked difference in the potencies of the two LPS preparations, and approximately 1,000-fold-higher concentrations of *H. pylori* LPS were required to achieve the same degree of monocyte activation.

*H. pylori* LPS does not upregulate endothelial-cell ICAM-1 expression. Both IL-1β (25 ng/ml) (Fig. 5) and *S. minnesota* lipid A (1 ng/ml; data not shown) caused a significant increase in endothelial-cell surface ICAM-1. In contrast, neither *H. pylori* LPS (100 ng/ml) nor HPE (30%) directly upregulated ICAM-1 levels. However, when conditioned medium from HPE-exposed monocytes was added to the endothelial-cell monolayer, it caused a marked increase in endothelial ICAM-1 levels. This effect was not seen with conditioned medium from control, unstimulated monocytes.

LPS inhibitor RSLA blocks *H. pylori* extract-stimulated monocyte IL-8 production. Having demonstrated that HPE activates the release of the chemokines IL-8, ENA-78, and MCP-1 from human monocytes, we then focused on determining the mechanism(s) of this effect. In subsequent experiments we used IL-8 as an “indicator” chemokine, since chemokine secretion by monocytes follows a common pattern of regulation whereby NF-κB-mediated gene activation is quickly followed by increased chemokine protein production and release (7, 8, 23, 24, 49).

We next sought to determine the extent to which *H. pylori* LPS, present in the *H. pylori* water extract, was responsible for monocyte stimulation. RSLA is a structural analogue of LPS that acts as a competitive antagonist to *S. minnesota* lipid A and to the LPS of other gram-negative bacilli. We first deter-
mined whether RSLA was an effective inhibitor of *H. pylori* LPS. As illustrated in Fig. 6, RSLA caused a dose-dependent inhibition of IL-8 release by monocytes exposed to *H. pylori* LPS at 100 ng/ml. RSLA concentrations of 10 and 100 μg/ml reduced *H. pylori* LPS-stimulated IL-8 production by 85% (*P*, 0.01). RSLA alone did not cause any significant alteration in IL-8 production by unstimulated monocytes (Fig. 6).

RSLA also blocked HPE-stimulated IL-8 release (Fig. 7). RSLA (1 μg/ml) completely prevented the upregulation of IL-8 release by monocytes exposed to HPE at concentrations of 0.1% and 1%. HPE 10% caused a marked increase in monocyte IL-8 release that was inhibited by 93% in the presence of RSLA (Fig. 7).

Since LPS is heat stable, we also studied whether heating HPE (100°C for 15 min) would alter its ability to stimulate chemokine release by monocytes. Heat treatment did not reduce monocyte activation by HPE (Fig. 8). Furthermore, RSLA blocked monocyte activation by heat-treated HPE to a degree similar to that produced by untreated HPE.

**FIG. 4.** *H. pylori* LPS has low potency in stimulating monocyte IL-8 release. Human monocytes were exposed to various concentrations of *H. pylori* LPS or to *S. minnesota* lipid A, and the IL-8 levels were measured by ELISA in conditioned media harvested after 18 h. In this representative experiment, *n* = 3 for each condition. Results are expressed as means ± SE. The IL-8 levels were 0.15 ± 0.02 ng/ml in control monocytes.

**FIG. 5.** *H. pylori* LPS and HPE do not directly upregulate endothelial-cell ICAM-1 expression. Human endothelial cells were exposed to IL-1β (25 ng/ml), *H. pylori* LPS (100 ng/ml), HPE (30% concentration), and to conditioned medium from either control or HPE-stimulated monocytes. Endothelial-cell ICAM-1 surface expression was evaluated after 18 h by cell-ELISA. In this representative experiment, *n* was ≥3 for each condition. The results are expressed as means ± SE. *P*, < 0.001 versus control.

**FIG. 6.** RSLA blocks the ability of *H. pylori* LPS to stimulate monocyte IL-8 production. Human monocytes were exposed to various concentrations of RSLA in the presence or absence of *H. pylori* LPS (100 ng/ml) or *S. minnesota* lipid A (1 ng/ml). The IL-8 levels were measured by ELISA in the conditioned media harvested after 18 h. In this representative experiment, *n* = 3 for each condition. The results are expressed as means ± SE. For the *H. pylori* LPS series, *P* denotes *P*, 0.01 compared to *H. pylori* LPS alone (i.e., 0 μg of RSLA per ml).

**FIG. 7.** The LPS inhibitor RSLA blocks the ability of HPE to stimulate monocyte IL-8 production. Human monocytes were exposed to various concentrations of HPE alone or with RSLA (1 μg/ml). The IL-8 levels were measured by ELISA in conditioned media harvested after 18 h. In this representative experiment, *n* = 4 for each condition. The results are expressed as means ± SE. *P*, < 0.01 compared to the same concentration of HPE alone (Student’s *t* test).
a significant effect on IL-8 release by unstimulated monocytes (Fig. 9). 60bca, but not 26iC, blocked monocyte activation by H. pylori LPS (10 µg/ml, 89% inhibition, P < 0.01). 60bca also blocked HPE-stimulated IL-8 release to a similar extent (84% inhibition, P < 0.01).

DISCUSSION

Our studies demonstrate that H. pylori LPS stimulates the release of both neutrophil-activating, C-X-C chemokines (IL-8 and ENA-78) and the monocyte-activating C-C chemokine MCP-1 from human monocytes. These chemokines are potent leukocyte chemoattractants and may play an important role in regulating inflammatory cell infiltration of H. pylori-infected gastric mucosa (7, 11, 14, 15, 20, 21, 23, 27, 37, 40, 48). We found that H. pylori LPS is less potent than Salmonella lipid A in inducing monocyte chemokine production. This finding agrees with previous studies showing low potency for H. pylori LPS in the induction of a wide variety of host inflammatory responses (9, 18, 19, 34, 36, 38, 39, 42). However, when the actions of H. pylori LPS were specifically inhibited by using either an LPS antagonist or CD14 receptor blockade, the monocyte-activating potential of H. pylori water extract was almost completely abolished. These findings suggest that H. pylori LPS may be the primary monocyte-activating factor present in H. pylori water extract.

The monoclonal antibody 60bca binds to CD14 and blocks LPS-CD14 interaction (51). This antibody markedly inhibited activation of human monocytes by both purified H. pylori LPS and H. pylori water extract. The nonblocking anti-CD14 monomonal antibody 26iC had no significant effect. These findings confirm that H. pylori LPS, in common with LPS from Enterobacteriaceae, activates human monocytes through CD14 receptor binding. This agrees with a recent study demonstrating that CD14 and LPS-binding protein were required for maximal activation of 70Z/3 cells by H. pylori LPS (29). Binding of LPS to CD14 is greatly enhanced by the attachment of LPS binding protein to LPS. Cunningham et al. reported that H. pylori LPS transfers very slowly from LPS binding protein to recombinant soluble CD14 and suggest that this may be an important factor in determining the low biological potency of H. pylori LPS (18).

A number of studies report that gastric mucosal levels of IL-8 are increased in patients with H. pylori gastritis (13–15, 21, 23, 37, 52). More recently, increased expression of ENA-78 mRNA was also described in H. pylori infection and appeared to correlate with the severity of gastritis (44). Both IL-8 and ENA-78 are produced by gastrointestinal epithelial cells, as well as by monocytes and macrophages (7, 8, 13–15, 17, 23, 24, 48, 49). Activation of epithelial cell IL-8 and ENA-78 production seems to require contact between live H. pylori and the gastric epithelial cell (1, 17, 23, 45). H. pylori LPS shows little activity in stimulating epithelial cells, possibly reflecting their lack of CD14 expression. This is in contrast to human monocytes and macrophages, which highly express CD14. These findings indicate appropriate differentiation of immune responsiveness whereby the gastric epithelial cell responds only to direct contact with H. pylori, whereas lamina propria cells respond to soluble bacterial products which, in vivo, would signal a breach in the integrity of the epithelial barrier.

Chemokines provide a chemoattractant signal to direct neutrophil migration toward an inflammatory focus. However, endothelial cell activation is required also for neutrophils to adhere to the vascular endothelium, migrate between endothelial cell tight junctions, and infiltrate tissues (8, 17, 19, 25, 41). This led us to examine whether HPE could also activate endothelial cells and upregulate their expression of the adhesion molecule ICAM-1. ICAM-1 binds to neutrophil β2 integrin adhesion receptors, a necessary step in neutrophil diapedesis. We find that HPE does not upregulate directly human endothelial cell ICAM-1 expression in vitro. However, activation of monocytes by HPE results in the release of monocyte-derived factors which can increase endothelial cell ICAM-1 expression, thereby facilitating leukocyte infiltration of the gastric lamina propria.

Because of its low potency, H. pylori LPS had been considered to play a minor role in disease pathogenesis. However, it is now known that the O antigen region of H. pylori LPS

FIG. 8. The monocyte-activating factor in HPE is heat stable. Human monocytes were exposed to HPE (10% concentration) or to the same concentration of heat-treated HPE (100°C for 15 min) in the presence or absence of RSLA (1 µg/ml). The IL-8 levels were measured by ELISA in conditioned media harvested after 18 h. In this representative experiment, n = 4 for each condition. The results are expressed as means ± SE. *, P < 0.05; **, P < 0.01 (versus the corresponding no antibody group).

FIG. 9. The monocyte-activating factor in HPE uses the CD14 receptor. Human monocytes were exposed to S. minnesota lipid A (Sal LA), H. pylori LPS (HP LPS; 10 µg/ml), or HPE ( Hp extract; 10% concentration) alone or in the presence of either 26iC (a nonblocking anti-CD14 monoclonal antibody, 10 µg/ml) or 60bca (a blocking anti-CD14 monoclonal antibody, 10 µg/ml). The IL-8 levels were measured by ELISA in conditioned media harvested after 18 h. In this representative experiment, n = 4 for each condition. The results are expressed as means ± SE. *, P < 0.05; **, P < 0.01 (versus the corresponding no antibody group).
contains extended chains with N-acetylated-lactosamine units that may mimic the human cell surface glycoconjugates Lewisx and Lewisβ (6, 35, 50). These antigens may act as a cloak to allow H. pylori to escape host immune surveillance. However, antigenic mimicry by H. pylori LPS may also incite an autoimmune response, resulting in gastric mucosal injury (5). H. pylori LPS causes an acute gastritis and results in the induction of gastric epithelial cell apoptosis (43). Another recent study found severe atrophic gastritis in C57/Hej mice 6 months after infection with H. pylori. In contrast, no atrophy was found in H. pylori-infected C57/Hej mice, which are unresponsive to LPS (46). The main difference observed between the LPS-responsive and nonresponsive mouse strains in this study was a lack of macrophage infiltration of the lamina propria in the latter group. Our studies examined peripheral blood monocytes and may not be directly relevant to gastric lamina propria macrophages. However, our findings suggest that H. pylori LPS is an important virulence factor that plays a key role in CD14-mediated monocyte activation and inflammatory cell recruitment in H. pylori gastritis.

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