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Helicobacter pylori Lipopolysaccharide as a Possible Pathogenic Factor for Gastric Carcinogenesis

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1. Introduction

Helicobacter pylori is now recognized as being a causative factor of gastroduodenal diseases such as chronic gastritis, gastric ulcer, duodenal ulcer, gastric cancer and gastric low-grade mucosa-associated lymphoma tissue (MALT). Long-term persistent inflammation, injury and reconstitution of gastric mucosa, and immunological reactions against the infected *H. pylori* are thought to be the causes of lesion formation. Various causative factors of *H. pylori* for inflammation and injury of gastric mucosa have been proposed. The most studied bacterial pathogenic factors are vacuolating toxin (VacA) produced by *H. pylori*, ammonium ion generated by *H. pylori* urease, and monochloramines formed from hypochlorite produced by phagocytic cells and the ammonium ion (Hofman et al., 2004; Xia & Talley, 2001). These agents cause directly injury to the host gastric mucosa. Proinflammatory cytokines, such as interleukin (IL)-1, tumor necrosis factor-α (TNF-α), IL-6 and IL-8, are also induced by *H. pylori*. *H. pylori* activates the transcription factor NF-κB, which has a key role on inducing various inflammatory reaction including cytokine production, through type IV secretion system (Glocker et al., 1998). The type IV secretion system consisits of proteins encoded by genes located on *cag* pathogenicity island.

In addition, lipopolysaccharide (LPS) is believed to contribute to the pathogenicity of this bacterium. LPS is a major component of Gram-negative bacterial outer membrane. It is known as an endotoxin and is a strong inducer of inflammatory reaction. *H. pylori* LPS, however, has much lower endotoxic activity than that of other typical Gram-negative bacteria, such as member of the *Enterobacteriaceae* family (Matsuyama et al., 2001; Muotiala et al., 1992; Nielsen et al., 1994; Perez-Perez et al., 1995; Semeraro et al., 1996). Strong endotoxin at infection sites, such as the systemic circulation system and digestive tract, should lead to sepsis, namely systemic inflammatory response syndrome (SIRS), and severe local inflammation, respectively. The weak endotoxic activity is considered to be important for chronic infection. Weakly endotoxic LPSs are also reported for *Chlamydia/Chlamydophila* (Heine et al., 2003) and *Porphyromonas gingivalis* (Ogawa et al., 2000). These bacteria commonly infected humans chronically.

Typical LPS acts as a pathogen-associated molecular pattern (PAMP). PAMPs are recognized by pattern recognition receptors (PRRs) of which the most studies are the Toll-

like receptors (TLRs). Typical highly endotoxic LPS are recognized by the TLR4/MD2/CD14 complex, whereas the TLR that recognizes the weakly exdotoxic *H. pylori* LPS is controversial as discussed below. Bacterial flagella also act as a PAMP, and they are recognized by TLR5. Like the LPS, *H. pylori* flagella also show less activity as a TLR5 agonist (Andersen-Nissen et al., 2005). The PAMPs of *H. pylori*, therefore, share low potency as TLR agonists, namely they are weak inducers of inflammation.

In addition to low endotoxic activity, *H. pylori* LPS has several unique features, for example structures that mimic host Lewis blood group antigens (Moran, 2008). In this review, the chemical characteristics, biological activities, and role in gastric carcinogenesis of *H. pylori* LPS will be described. In particular we will focus on our recent research into LPS as a pathogenic factor for carcinogenesis.

2. General architecture of *H. pylori* LPS

Like other typical bacterial LPS, *H. pylori* LPS consists of three region, namely lipid A, core oligosaccharide and O-polysaccharide (Fig. 1). The weakly endotoxic activity is due to the chemical structure of lipid A portion. In *H. pylori* LPS, the carbohydrate portion of lipid A consists of a glucosaminyl-β-1-6-glucosamine disaccharide backbone, as well as the typical lipid A. Whereas the lipid A of typical LPS derived from *E. coli* contains six fatty acid residues with relatively short carbon chain, such as C14 and C12, *H. pylori* lipid A contains three to five fatty acids with long carbon chain of C18 and C16 (Moran et al., 1997; Suda et al., 1997). Netea et al. (2002) describe that the molecular shapes, such as conical, cylindrical and intermediate, of lipid A are different between the highly endotoxic typical LPS and the weakly endotoxic LPS. The diversity of molecular shapes may cause the difference of endotoxic activity and usage of TLRs. Remodeling of lipid A structures occur in *H. pylori* by the action of phosphatase, ethanolamine phosphate transferase, 3-deoxy-D-*manno*-octulosonic acid (KDO) hydrolase and deacylase (Tran et al., 2005). Hildebrandt & McGee (2009) report structural modifications of lipid A occur in an exogenous cholesterol-dependent manner. Thus lipid A structures may vary among strains or change depending on culture conditions.
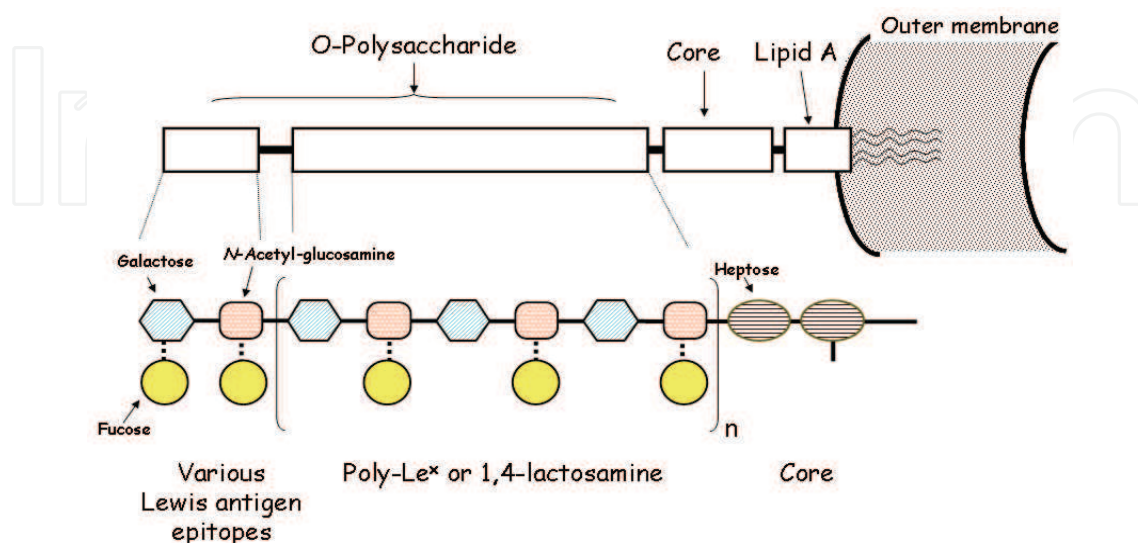

Fig. 1. General architecture of *H. pylori* LPS

The core oligosaccharide region of *H. pylori* LPS has a characteristic structure among *H. pylori* strains, however, the detailed structure is distinct from the typical LPS (Aspinall et al., 1997; Monteiro, 2001). It contains KDO and heptose residues similar to typical gram-negative bacterial LPS. There is some heterogeneity among *H. pylori* strains. For example, heptose oligomer (heptan) or glucose oligomer (glucan) is found in some strains.

One of the important features of *H. pylori* LPS is the O-polysaccharide region that bears the mimicking structures of the host carbohydrate antigens, Lewis antigens (Moran, 2008). It is interesting that *Campylobacter* species, which also belongs to spirillum, also shares host carbohydrate structures in gangliosides, such as GM1 and GQ1b (Yuki, 1999). Host Lewis antigens are recognized as a tumor antigen. Le^x is also known as CD15, which is a marker for neutrophils. The existence of Lewis antigens, such as Le^x, Le^y, Le^a and Le^b, varies among *H. pylori* strains. Lewis antigns are considered to contribute to escape from a host immune response and to induction of an autoimmune response. The O-polysaccharide of most *H. pylori* strains consists of a lactosamine (galacotosyl-β1-4-*N*-acetyl-glucosamine) unit as the backbone chain. L-Fucose residues are partially substituted in the backbone chain and form a polymeric Le^x structure. In addition, a high level of variability occurs in the non-reducing terminal end of the O-polysaccharide chain. For example, β1-3- or β1-4-linked galactose and α1-3- or α1-4-linked fucose can substitute on the *N*-acetyl-glucosamine residue, and α1-2-linked fucose can occur on the galactose residue. The variable substitutions form various Lewis antigen structures (Fig. 2).
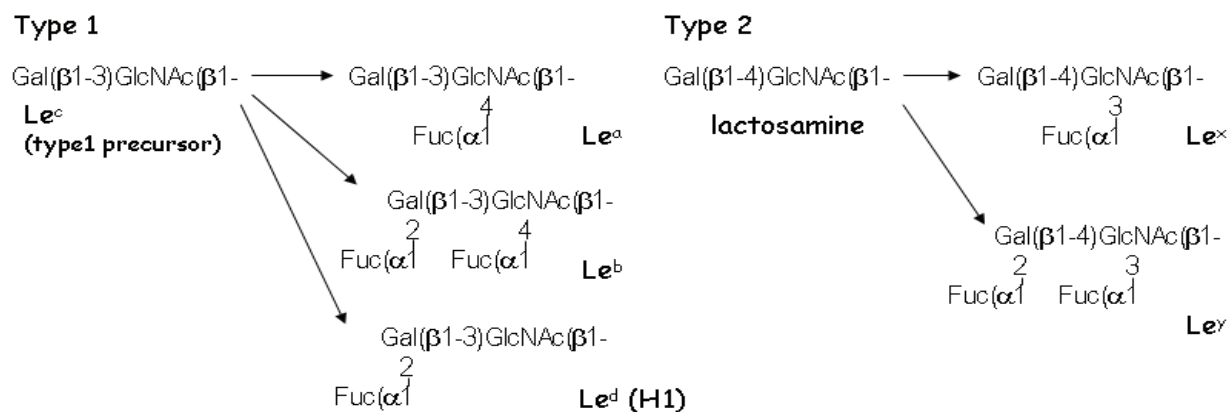

Fig. 2. Structures of Lewis antigens
Abbreviations. Fuc: L-fucose, Gal: D-galactose, GlcNAc: *N*-acetyl-D-glucosamine.

3. Biological roles of Lewis antigens *H. pylori* LPS

As described above, *H. pylori* Lewis antigens mimic host antigens and can thus modulate various host physiological responses, especially immunological reactions.

The O-polysaccharide, in particular the polymeric Le^x structure, has been shown to contribute to adhesion of *H. pylori* to human antral gastric mucosa. Galectin-3 is a gastric receptor for *H. pylori* Le^x antigen (Fowler et al., 2006). Lewis antigens can interact with other host lectins. Interaction with two particular C-type lectins is important for the modulation of

immunological responses. One is Dendritic Cell Specific ICAM-3 Grabbing Non-integrin (DC-SIGN; CD209). Whereas Lewis antigen-negative *H. pylori* cells predominantly promotes a strong Th1 cell response, Lewis antigen-bearing cells interact with DC-SIGN on dendritic cells and induce IL-10, which promotes a Th2 response in a mouse infection model (Bergman et al., 2004). The other C-type lectin that interact with *H. pylori* LPS is surfactant protein D (SP-D) (Khamri et al., 2005; Murray et al., 2002). SP-D is involved in antibody-independent clearance of bacteria. Levels of SP-D are increased in gastric mucosa with *H. pylori*-associated antral gastritis compared to normal gastric mucosa. The fucose residues of the O-polysaccharide chain are shown to be important for the recognition of SP-D. On the other hand, our recent study showed that D-galactose residue of *H. pylori* LPS is involved in interaction with SP-D as described below.

Another important issue is formation of anti-Lewis antigen autoantibodies. Anti-Le^y autoantibodies have been implicated in the pathogenesis of atrophic gastritis. The anti-Le^y autoantiboides are found both in patients with atrophic gastritis and gastric cancer (Heneghan et al., 2001; Negrini et al., 1996). A candidate for the target of the autoantibodies is the β-chain of the H$^+$,K$^+$-ATPase, which is a proton pump (Appelmelk et al., 1996). Anti-Le^x autoantibodies are also found in *H. pylori*-infected patients (Heneghan et al., 2001; Negrini et al., 1996). Anti-Le^x antibodies have been shown to activate neutrophils and enhance their adhesion to endothelium (Stockl et al., 1993) which could lead to inflammation and tissue damage. However, these antibodies induced by *H. pylori* do not react with synthetic Lewis antigens (Amano et al., 1997; Heneghan et al., 2001). The actual specificity of the anti-Lewis antigen antibodies has not been clear yet.

4. Antigenic epitopes of *H. pylori* LPS

Whereas anti-Lewis antigen autoantibodies have been shown to be raised in response to *H. pylori* infection and to contribute to generation of diseases, we did not found significantly increased levels of any anti-Lewis antigen antibodies in *H. pylori*-infected gastroduodenal disease patients, *H. pylori*-positive individuals, and *H. pylori*-negative individuals (Amano et al., 1997). The reactivity of human antisera to *H. pylori* LPS derived from various strains was examined and a classification of *H. pylori* LPS has been proposed based on the antigenicity of O-polysaccharides to humans, namely highly-antigenic-epitope-carrying LPS and weakly-antigenic-epitope-carrying LPS (Yokota et al., 1998; Yokota et al., 2000b). The two epitopes were clearly characterized by examining serum absorption by LPS (Fig. 3). All *H. pylori* strains carrying the O-polysaccharide chain (namely, smooth strains) isolated in Japan have either one or the other epitope, but not both. The existence of these epitopes does not relate to that of the Lewis antigen structures. Most (over 95%) of *H. pylori*-infected individuals, including gastroduodenal patients and asymptomatic individuals, have a high titer of antibodies against the anti-highly-antigenic epitope in their sera. It is therefore proposed that the highly-antigenic epitope-carrying LPS are applicable to diagnosis of *H. pylori* infection (Amano et al., 1998) (Table 1). As an advantage, the LPS antigen is more stable against heat, drying and humidity than protein antigens. On the other hand, about half of *H. pylori*-infected individuals have antibodies against the weakly-antigenic epitope at a lower titer than those against the highly-antigenic epitope. The antibody titer against the weakly-antigenic epitope is significantly higher in gastroduodenal patients than in asymptomatic individuals with *H. pylori* infection (Yokota et al., 2000a). The antibodies against the weakly-antigenic epitope could relate to chronic and active infection of *H. pylori*.

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Human serum containing:	No. of sera
anti-highly antigenic epitope antibody only	31 (52.5%)
anti-weakly antigenic epitope antibody only	4 (6.8%)
both antibodies	24 (40.7%)

Table 1. Frequency of anti-*H. pylori* LPS epitope antibodies in 59 sera derived from *H. pylori*-infected individuals.
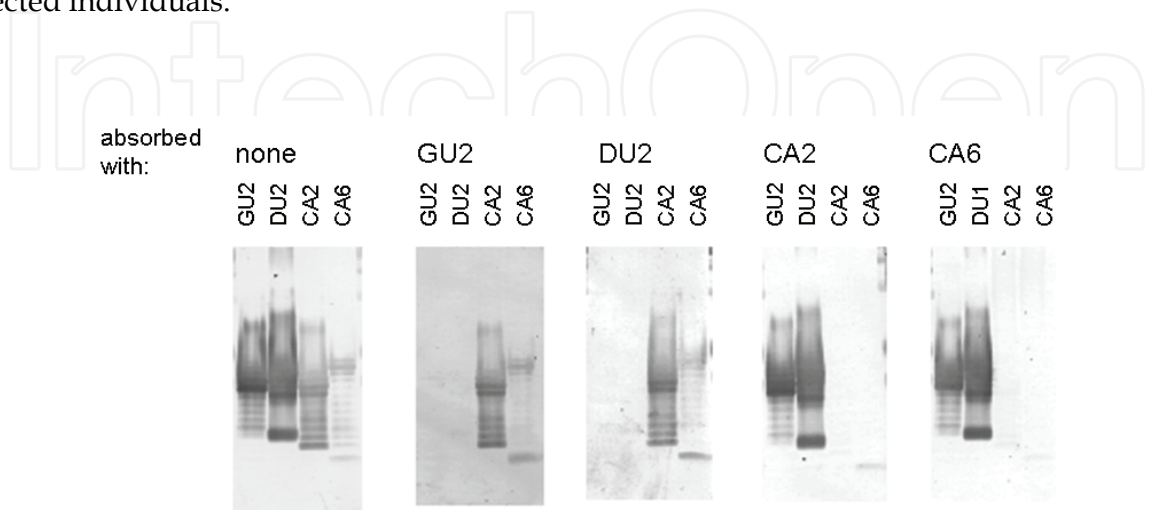

Fig. 3. Reactivity of human serum containing antibodies against both highly-antigenic epitope and weakly-antigenic epitope in *H. pylori* LPS determined by Western blotting and absorption with LPS.

Serum from one individual containing antibodies against both epitopes was absorbed with the indicated LPS at 37 C for 1 h, and used in Western blotting. LPS derived from strains GU2 and DU2 are highly-antigenic epitope-containing. LPS derived from strains CA2 and CA6 are weakly-antigenic epitope-containing.

5. Usage of TLRs by *H. pylori* LPS

TLR usage by *H. pylori* LPS remains controversial. An important issue to consider in these kinds of studies is the presence of contaminants with endotoxin-like activities, for example lipopeptides of *H. pylori* and other bacterial LPS, in the *H. pylori* LPS preparations. The extremely low level activity of *H. pylori* LPS means that very low level contamination cannot be ignored. Alternatively, as described above, structural heterogeneity exists in *H. pylori* lipid A and therefore different TLR usage could depend on lipid A structural variation.

Whereas the weakly endotoxic activity of *H. pylori* LPS is widely accepted, TLR usage has been controversial with some researchers reporting that *H. pylori* LPS transduces signaling via the TLR4/MD2/CD14 complex like a typical LPS and others reporting signaling transduction via TLR2 as summarized in Table 2. Another report describes antagonistic activity of *H. pylori* LPS derived from some strains to TLR4-mediated typical LPS signaling (Lepper et al., 2005).

Strains having the highly-antigenic epitope-carrying LPS are frequently found in those derived from patients with chronic gastritis. Strains having the weakly-antigenic epitope-carrying LPS are predominantly found in those derived from patients with gastric cancer (Yokota et al., 2000b; Yokota et al., 1997) (Fig. 4).

Report	Usage of TLR	*H. pylori* strain	Purification method of LPS	Experimental evidences
Kawahara et al,(2001)	TLR4	Various strains	Hot phenol water/ ultracentrifugation	Using primary gastric mucosa cells derived from guinea pig. The cells are negative for TLR2.
Ogawa et al. (2000), (2003)	TLR4	206-1	Synthetic lipid A	Using human peripheral blood mononuclear cells. The activities are neutralized by anti-TLR4 antibodies.
Ishihara et al. (2004)	TLR2	26695	Reextraction method described by (Hirschfeld et al., 2000)	Luciferase reporter gene assay using HEK293 cells transfected with TLRs.
Lepper et al. (2005)	TLR2	Various strains	Reextraction method described by (Hirschfeld et al., 2000)	Luciferase reporter gene assay using HEK293 and COS cells transfected with TLRs. LPS derived from some strains shares activity that antagonized TLR4.
Yokota et al. (2007)	TLR2	Various clinical isolates	Reextraction (treatment with proteinase K and lipoprotein lipases / HIC[a])	Luciferase reporter gene assay using HEK293 cells transfected with TLRs. Effect of the expression of dominant negative mutants of TLRs.
Chochi et al. (2008)	TLR4	A clinical isolate	Not described (donated from Ohtsuka Co.)	Using 4 gastric cancer cell lines. The activities are neutralized by anti-TLR4 antibodies.
Smith et al. (2011)	TLR2	3 reference strains and 4 clinical strains	Hot phenol water/proteinase K and nuclease treatment / ultracentrifugation	Using HEK293 cells transfected with TLR2. Using TLR2-negative gastric cell line AGS.

Table 2. Interaction between *H. pylori* LPS and TLRs.
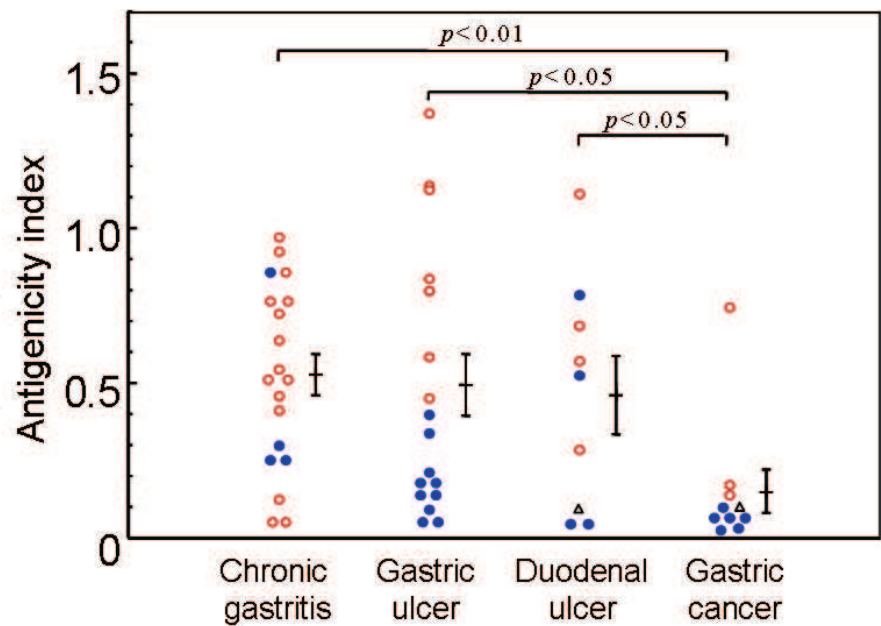[a]HIC: hydrophobic interaction chromatography.

Fig. 4. Antigenicity and antigenic type of *H. pylori* isolated from various clinical sources. Antigenicity index is expressed as the mean values of ELISA reading for 15 randomly selected serum samples from *H. pylori*-infected individuals. Red open circle: Strains with LPS carrying the highly-antigenic epitope. Blue close circle: Strains with LPS carrying the weakly-antigenic epitope. Triangle: Rough strains.

6. Novel biological activities of *H. pylori* LPS

While a consensus has gotten on that *H. pylori* LPS share low toxicity as an endotoxin, some important biological activities have been observed. Chochi et al. (2008) reported that both *H. pylori* and *E. coli* LPS enhance the proliferation rate of gastric cancer cell lines. However, they also showed that *H. pylori* LPS, but not *E. coli* LPS, attenuates the cytotoxicity of mononuclear cells against gastric cancer cells, and downregulates perforin production in CD56^{+} natural killer cells cocultured with gastric cancer cells. Both the mitogenic activity, in common with *E. coli*, and the *H. pylori*-specific decrease in cytotoxicity of natural killer cells are likely to promote tumorigenesis. Grebowska et al. report that *H. pylori* LPS suppress phagocytic activity of human peripheral blood granulocytes (Grebowska et al., 2008) and *H. pylori* LPS-chased macrophages have low activity of lymphocyte proliferation (Grebowska et al., 2010). They speculate that these activities contribute to chronic infection of *H pylori*.

Slomiany et al. reported that *H. pylori* LPS disrupts gastric mucin synthesis, increases caspase-3 activity, causes apoptosis, and upregulates endothelin-1 and TNF-α via p38 and ERK MAP kinase cascade activation (Slomiany et al., 1999; Slomiany & Slomiany, 2002). Furthermore, it inhibits glycation and sulfation in gastric mucin biosynthesis (Slomiany et al., 1992). Kawahara et al. (2001) reported that the LPS of *H. pylori*, as well as that of *E. coli*, upregulates mitogen oxidase 1 (Mox1), which leads to the generation of superoxide anions. Young et al. (1992) report that it stimulates gastric mucosal pepsinogen secretion. These are likely to lead to injury of gastric mucosa.

We found that pretreatment of gastric epithelial cell lines with *H. pylori* LPS enhanced the expression of TLR4 and also the responsiveness to *E. coli* LPS (Fig. 5-C) (Yokota et al., 2010). These gastric epithelial cell lines express markedly low levels of TLR4. *H. pylori* LPS
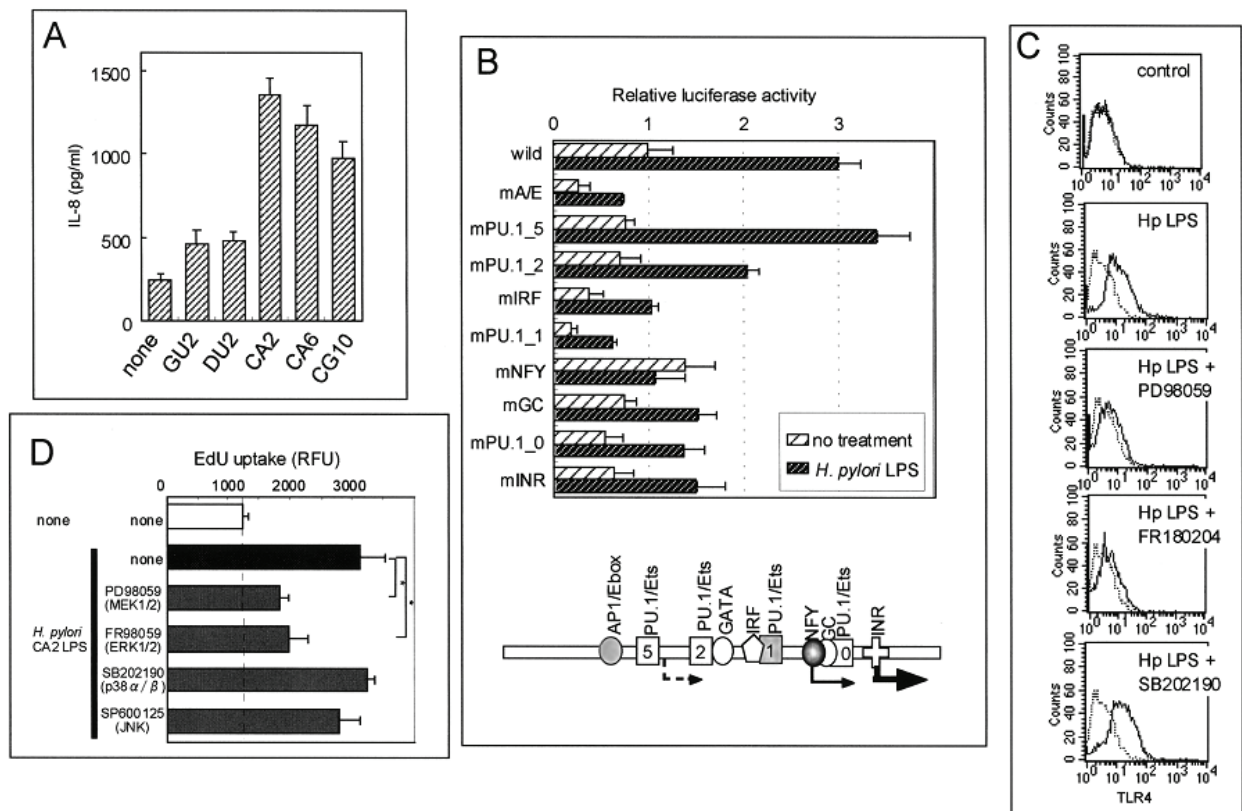
Fig. 5. A. Pretreatment with *H. pylori* LPS enhanced *E. coli* LPS-induced IL-8 production. Gastric cancer cell line MKN28 was treated with *H. pylori* LPS (100 ng/ml) for 24 h, then treated with *E. coli* LPS (1000 ng/ml) for 24 h, and IL-8 in the culture supernatants was measured by ELISA. LPS derived from GU2 and DU2 *H. pylori* strains is highly-antigenic epitope-carrying. LPS derived from CA2 and CA6 strains is weakly-antigenic LPS-carrying. LPS derived from CG10 strain is rough-type.

B. TLR4 promoter activity with *H. pylori* CA2 LPS treatment determined by the luciferase reporter assay. Luciferase gene-conjugated promoters with a series of mutations introduced in the transcription factor binding motifs indicated were used. NF-Y binding motif is indicated to be important for transcriptional induction of TLR4 by *H. pylori* LPS.

C. Enhancement of TLR4 expression by *H. pylori* LPS and effect of inhibitors for MAP kinases. MKN28 cells were treated with *H. pylori* CA2 LPS (100 ng/ml) for 24 h, and then TLR4 on the cell surface was analyzed by flow cytometry.

D. Enhancement of gastric epithelial cell growth by *H. pylori* LPS and effect of MAP kinase inhibitors. MKN28 cells were treated with *H. pylori* CA2 LPS (100 ng/ml) for 18 h, and then cell proliferation rate was measured by the uptake of 5-ethinyl-2'-deoxyuridine into DNA. MAP kinase inhibitors used were PD98059 (MEK1/2 inhibitor; 50 µM), FR180204 (ERK1/2 inhibitor; 5 µM), SB202190 (p38 inhibitor; 5 µM), and SP600125 (JNK inhibitor; 10 µM).
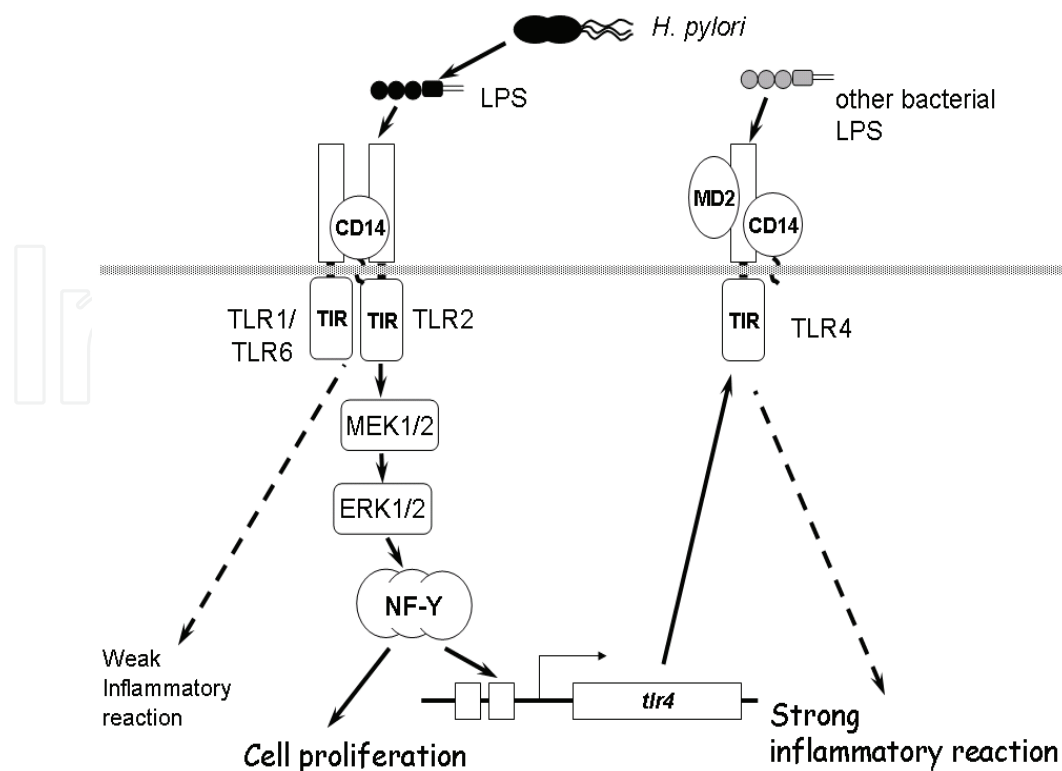
Fig. 6. Proposed action of *H. pylori* LPS on gastric epithelial cells.
H. pylori LPS upregulates TLR4 and augments cell proliferation via TLR2 and the MEK1/2-ERK1/2 MAP kinase pathway in gastric epithelial cells. These activities are likely to enhance the inflammatory response, by increasing the activity of highly endotoxic typical LPS derived from other bacteria, and tumorigenesis.

recognized by TLR2, preferentially as a TLR2/TLR1 complex, activated MEK-ERK MAP kinase cascade and the transcription factor NF-Y, and upregulated transcription of the TLR4 gene (Fig. 5-B). In consistent with the in vitro observation, Asahi et al. (2007) indicate that higher expression of TLR4 is observed in biopsy specimens in the antral and corpus mucosa from *H. pylori*-infected patients than *H. pylori*-negative individuals. Backhed et al. (2003) report that primary gastric antral cells do not express TLR4, in contrast, several epithelial cell lines derived form gastric cancer do. The upregulated TLR4 in the gastric epithelial cells causes more efficient transduction of inflammatory signals by typical LPS, such as LPS derived from *Enterobacteriaceae* (Fig. 5-A).
In concordance with the report of Chochi et al. (2008), *H. pylori* LPS was shown to upregulate the cell growth rate of gastric epithelial cell lines (Yokota et al., 2010) (Fig. 5-D). Activation of the MEK-ERK MAP kinase pathway via TLR2 activates NF-Y, and the NF-Y transcriptionally activates various cell cycle regulation genes, such as cyclin A1, cyclin B2, and E2F1. However, there are some contradictions between our report (Yokota et al., 2010) and the report of Chochi et al. (2008). We found that the mitogenic activity was *H. pylori*-specific. With respect to TLR usage, Chochi et al. (2008) showed that anti-TLR4 antibody can neutralize the activity; however, we found that downregulation of TLR2 expression by siRNA diminished the activity (Yokota et al., 2010).
The novel activities of *H. pylori* LPS reported by us (Yokota et al., 2010) (Fig. 6) are more potent in weakly-antigenic epitope-carrying LPS frequently isolated from gastric cancer,

than in highly-antigenic LPS-carrying strains. The weakly-antigenic LPS-carrying *H. pylori* strains are suggested to be more potent inducers of gastric cancer. The potent activities of the weakly-antigenic LPS may be due to interaction of *H. pylori* LPS with host SP-D. A recent study indicates that SP-D enhances *E. coli* LPS-induced proinflammatory cytokine production upregulated by *H. pylori* LPS pretreatment (Yokota et al. unpublished results). SP-D interacts more strongly with weakly-antigenic epitope-carrying LPS than highly-antigenic epitope-carrying LPS. The β-linked *N*-acetyl-glucosamine residue is suggested to be important for the highly-antigenic epitope, and digestion of the residue by a β-*N*-acetyl-glucosamindase abolished the reactivity with anti-highly antigenic epitope antibody and appeared reactivity with anti-weakly antigenic epiotpe antibodies (Yokota et al., unpublished results). The β-galacotose residue is implicated in the weakly antigenic epitope and interaction with SP-D.

7. Concluding remarks

We propose the existence of two antigenic epitopes in *H. pylori* LPS. One of these, the weakly-antigenic epiotpe-carrying LPS, appears to occur frequently in strains derived from gastric cancer patients, as compared with chronic gastritis patients. The anti-weakly-antigenic epitope antibody titers are higher in gastroduodenal patients than in asymptomatic *H. pylori*-infected individuals. The weakly-antigenic epitope-carrying LPS has stronger biological activity than the highly-antigenic epitope-carrying LPS. From these lines of evidence, strains carrying highly-antigenic epitope may change to strains carrying weakly-antigenic epitope during infection periods and disease progression status (Fig. 7). This phenotypic change leads to an escape strategy for *H. pylori* from host immune response
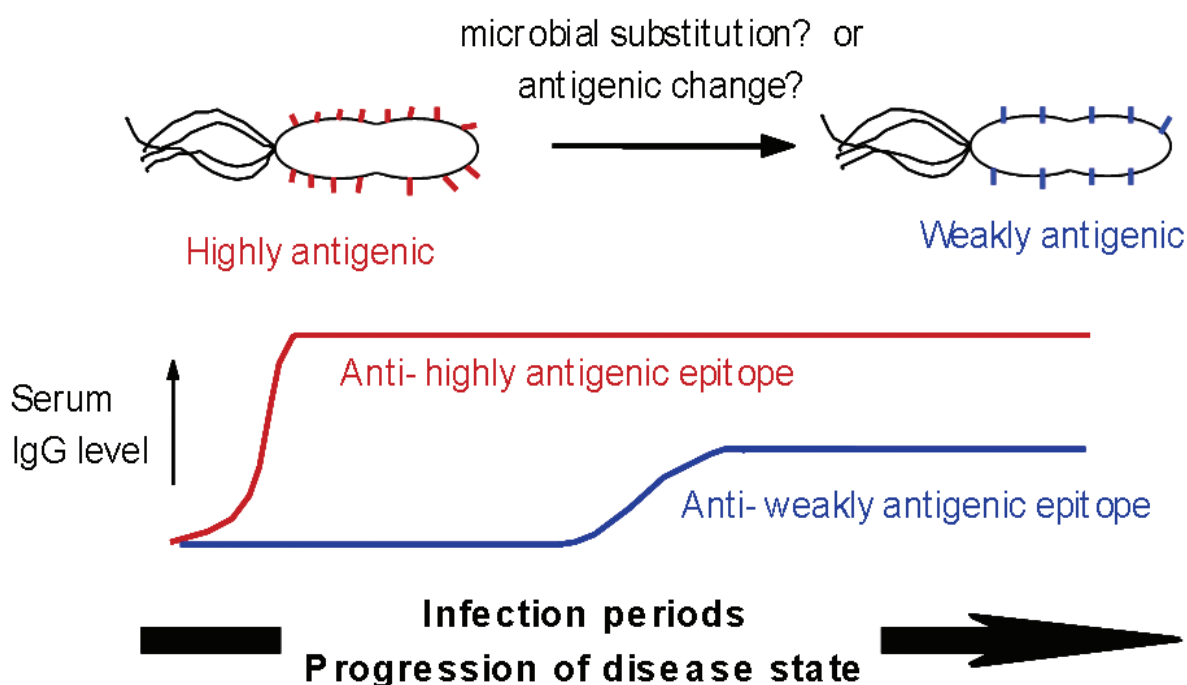

Fig. 7. Relationship between changes of antigenic epitopes of *H. pylori* LPS, serum antibody titers to *H. pylori* LPS epitopes, and infection periods.

and to an increase in virulence. It is not clear whether the phenotypic change occurs by antigenic change of one strain or by microbial substitution. But the presence or not of a β-*N*-acetyl-glucosamine residue of the polysaccharide chain of LPS appears to determine the antigenic conversion. Molecular studies of biosynthesis of LPS, for example glycosyltransferase expressions, are now required to elucidate these changes.

We propose that *H. pylori* LPS enhances the inflammatory reaction induced by other bacterial LPS and upregulates the growth rate of epithelial cells via activation of the MEK1/2-ERK1/2 MAP kinase cascade. A putative role for *H. pylori* LPS as a pathogenic factor is shown in Fig. 8. In an *H. pylori*-uninfected gastric mucosa, Gram-negative bacteria invading orally do not cause a strong inflammatory response in gastric mucosa because the expression levels of TLR4 are low in gastric epithelial cells. On infection with *H. pylori*, *H. pylori* LPS upregulates TLR4 via TLR2 signaling in gastric epithelial cells. The upregulation of TLR4 leads to increased susceptibility of epithelial cells to typical LPS derived from other bacteria. Although the acids of gastric juice kill orally invading bacteria, LPS should be still stable. *H. pylori* LPS itself showed extremely weak endotoxic activity and therefore does not cause acute and systemic inflammatory reaction, such as sepsis. This strategy enables *H. pylori* to escape the host immune system and establish chronic infection. On the other hand, *H. pylori* LPS sets the stage for inflammatory response and tumorigenesis in the gastric mucosa during chronic infection, in other words, colonization.
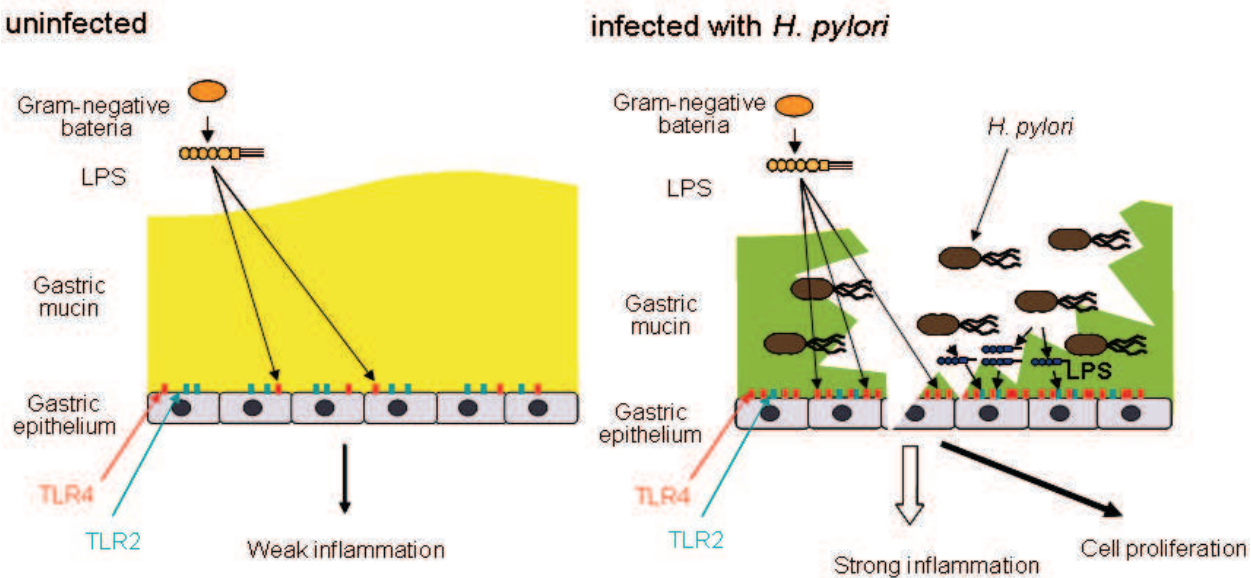

Fig. 8. Hypothesis for a pathogenic role of weakly-endotoxic *H. pylori* LPS in gastric mucosa. Uninfected state: Expression of TLR4 on the epithelial cells in gastric mucosa is low. So LPS derived from orally invaded bacteria does not induce a strong inflammatory response.
H. pylori-infected state: *H. pylori* LPS itself causes low-level direct inflammation and tissue injury. At the same time, *H. pylori* LPS induces TLR4 expression on the epithelial cells in gastric mucosa, and therefore LPS with high endotoxic activity derived from orally invading bacteria causes higher level inflammation than in the *H. pylori*-uninfected state.
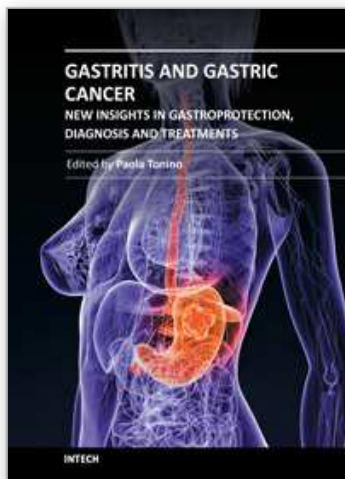
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This book is a comprehensive overview of invited contributions on Helicobacter pylori infection in gastritis and gastric carcinogenesis. The first part of the book covers topics related to the pathophysiology of gastric mucosal defense system and gastritis including the gastroprotective function of the mucus, the capsaicin-sensitive afferent nerves and the oxidative stress pathway involved in inflammation, apoptosis and autophagy in H. pylori related gastritis. The next chapters deal with molecular pathogenesis and treatment, which consider the role of neuroendocrine cells in gastric disease, DNA methylation in H. pylori infection, the role of antioxidants and phytotherapy in gastric disease. The final part presents the effects of cancer risk factors associated with H. pylori infection. These chapters discuss the serum pepsinogen test, K-ras mutations, cell kinetics, and H. pylori lipopolysaccharide, as well as the roles of several bacterial genes (cagA, cagT, vacA and dupA) as virulence factors in gastric cancer, and the gastrokine-1 protein in cancer progression.

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