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TOPIC HIGHLIGHT

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Novel role of toll-like receptors in *Helicobacter pylori* - induced gastric malignancy

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Abstract

Helicobacter pylori (*H. pylori*) infects the human stomach during infancy and develops into chronic active inflammation. The majority of *H. pylori* tend to colonize within the mucous gel layer of the stomach. The stomach lacks its own immune function, thus innate immunity as the first line of defense is vital for specific immunity against *H. pylori*. We review recent discoveries in the pathophysiologic roles of toll-like receptors (TLRs), mainly TLR2 and TLR4, in *H. pylori*-induced inflammation. In addition, the TLR pathways activated by *H. pylori*-induced inflammation have been shown to be closely associated not only with gastric carcinogenesis, but also with formation of the tumor microenvironment through the production of pro-inflammatory cytokines, chemokines, and reactive oxygen species. Although the correlation between single nucleotide polymorphisms of TLRs and gastric cancer risk remains unclear, a recent study demonstrated that STAT3-driven up-regulation of TLR2 might promote gastric tumorigenesis independent of inflammation. Further research on the regulation of TLRs in *H. pylori*-associated gastric carcinogenesis will uncover diagnostic/predictive biomarkers and therapeutic targets for gastric cancer.

Key words: Toll like receptors; *Helicobacter pylori*; Gastric cancer; Pathogen-associated molecular patterns; Damage-associated molecular patterns

Core tip: Toll-like receptors (TLRs) play important roles not only in the first line of defense against *Helicobacter pylori* (*H. pylori*), but also in gastric carcinogenesis. TLR signaling initiated by pathogen-associated molecular patterns of *H. pylori* consequently works to establish antigen-specific acquired immune responses. Simultaneously, damage-associated molecular patterns produced by chronic inflammation may contribute to gastric cancer development. A better understanding of TLRs will provide new insights into new diagnostic/predictive biomarkers and therapeutic targets for *H. pylori*-associated gastric cancer.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative, spiral-shaped, microaerophilic bacteria which infects the human stomach during infancy. The majority of *H. pylori* tend to colonize within the mucous gel layer of the stomach and result in life-long inflammation in the human gastric mucosa[1-3]. A variety of gastric diseases, including peptic ulcers, gastric mucosa-associated lymphoid tissue lymphomas and gastric cancers, are strongly associated with *H. pylori*-induced gastritis[1,2].

A distinguishing characteristic of *H. pylori*-induced gastritis is chronic active inflammation, which consists of intraepithelial infiltration of neutrophils and acquired immune response by adaptive T helper type 1 lymphocytes[4]. The production of cytokine-associated gene A protein and vacuolating toxin are reported to be the major virulence factors of *H. pylori*, and harmful alterations can occur when the microbe directly interacts with the gastric epithelium[5-9]. These intra-bacterial virulent factors can evoke active inflammation to ward off the infection, but most *H. pylori* infections progress to chronic gastritis due to the specific immune response against *H. pylori*. In fact, not all *H. pylori* strains harbor these intra-bacterial factors, and less than 20% of the bacterial population binds to gastric epithelial cells[3]. Furthermore, the stomach lacks intraepithelial T lymphocytes and a coordinating lymph system[10]. These issues lead to the question of how the human stomach acquires adaptive immunity towards *H. pylori*?

All human beings have innate immunity, which serves as a first line of defense against foreign agents. This innate immunity is able to discriminate quickly between self and microbial non-self in a non-specific manner[11], and maintain mucosal homeostasis by recruiting immune cells and activating additional immune responses[12]. Thus, the innate immunity within gastric mucosa is vital to the establishment of adaptive immune responses against *H. pylori*. In this review, we aim to clarify recent discoveries in the role of pattern recognition systems in the innate immunity against *H. pylori*-related carcinogenesis.

TOLL-LIKE RECEPTORS IN INNATE IMMUNITY

Toll-like receptors (TLRs) are important pattern recognition receptors on cellular surfaces in the innate immune system[13]. TLRs are characterized by N-terminal leucine-rich repeats, a trans-membrane region and a cytoplasmic toll/interleukin (IL)-1R homology (TIR) domain. TLRs can sense structurally conserved molecules (pathogen-associated molecular patterns, PAMPs), such as lipopolysaccharide (LPS), peptidoglycan, lipoteichoic acid, lipoprotein, and unmethylated DNA with a CpG motif, from invading pathogens outside of the cell and in intracellular endosomes and lysosomes[14,15]. Although thirteen TLRs have been discovered in mammals, ten types of TLRs have been identified in humans. The intracellular signal propagation of human TLRs and their representative ligands are described in Figure 1[14-16].

TLR ligands (TLRs bound to their specific ligand) transmit signals through myeloid differentiation primary response protein-88 (MyD88), TIR domain, and tumor necrosis receptor associated factor 6 (TRAF6). Downstream signaling pathways then activate phosphorylation of inhibitor of kappa B kinase (IKK) enzyme complex and mitogen activated protein (MAP) kinases. Eventually, nuclear factor-kappa B (NF-κB) activation translocates the nucleus for transcription of pro-inflammatory genes, such as inflammatory cytokines, type- I interferon (IFN), and chemokines in the inflammation[17-19]. Additionally, these signaling cascades can induce several co-stimulatory molecules, essential for initiation of adaptive immune responses in the host[20].

A new discovery is that TLRs are also able to recognize damage-associated molecular patterns (DAMPs) as endogenous ligands produced under stress conditions, such as heat-shock protein 60, extra domain A of fibronectin, hyaluronan fragments, chromatin-associated protein high-mobility group box 1, and neutrophil activating protein (NAP)[21-23]. The recognition of DAMPs accordingly directs the wide-ranging responsiveness of TLRs not only to foreign agents, but also to internal organisms denatured by inflammation.

ROLE OF TLRS IN INNATE IMMUNITY AGAINST *H. PYLORI* IN GASTRIC MUCOSA

Previous studies using an inflammatory cDNA array assay demonstrated strong involvement of TLRs, along with adhesion molecules, chemokines, and interleukins, in the mucosal response in *H. pylori*-associated gastritis[24].

H. pylori is a gram-negative bacteria; therefore, *H. pylori*-derived LPS is considered a direct stimulator of TLR4-mediated innate immunity (Figure 2). Previous immunohistochemical studies revealed that the expression of TLR4 in *H. pylori* gastritis was higher than that in uninfected gastric mucosa. The increased expression of TLR4 at the apical site of gastric epithelial cells was also characteristic of *H. pylori*-infected epithelium in comparison to the basolateral site of non-inflamed gastric epithelial cells[25-29].

H. pylori-LPS initiates the NF-κB pathway through ligation with TLR4 and then activates the promoter of pro-inflammatory cytokines, such as the IL-8 pathway[26-30]. *H. pylori*-LPS has also been reported to promote gastric cancer through the TLR4 pathway with suppressive effects on the anti-tumor reaction of mononuclear cells[31].

However, the participation of TLR4 in gastric innate immunity against *H. pylori* infection is still controversial. Some studies demonstrated that *H. pylori*-LPS-induced production of inflammatory cytokines in gastric epithelial cells or human macrophages was independent of TLR4[32-34]. Contrary to expectations, *H. pylori*-LPS is a weak stimulus of the immune response in comparison to LPS from other gram-negative bacteria owing to the unique structure of lipid core A of *H. pylori*-LPS[35,36].

PARTICIPATION OF TLR2 IN *H. PYLORI*-INDUCED INNATE IMMUNITY

TLR2 can recognize a variety of PAMPs from gram-positive bacteria and mycobacteria[14,15], but TLR2 is believed to ligate different structures of LPS recognized

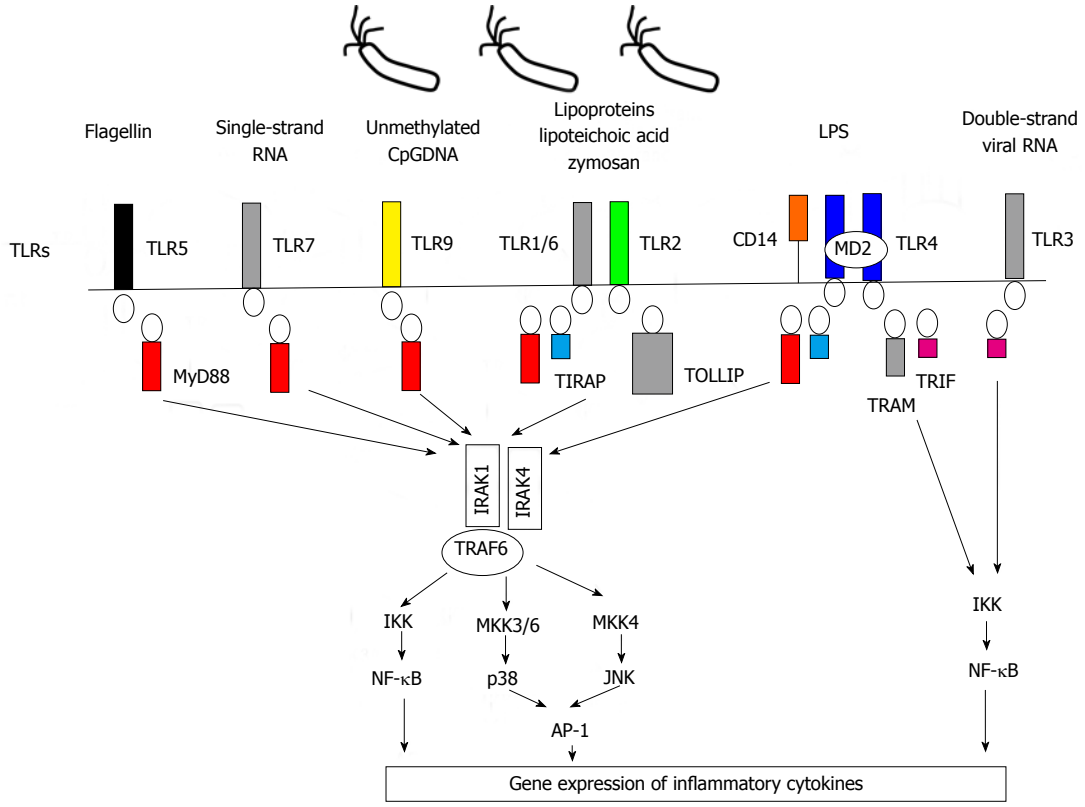

Figure 1 Intracellular signal propagation of human toll-like receptors and corresponding ligands in innate immunity. Toll-like receptors (TLRs) and ligands in human are revealed in the figure. Individual TLRs recognize specific (pathogen-associated molecular patterns, PAMPs) or damage-associated molecular patterns (DAMPs) of corresponding ligands. TLR signaling is propagated by activation of its cytoplasmic TIR (Toll/IL-1R) domain and cooperation with various adaptor molecules, such as myeloid differentiation factor 88 (MyD-88), toll-interleukin 1 receptor (TIR) domain-containing adapter protein (TIRAP), toll interacting protein (TOLLIP), (IRAK), (TRAF), TIR domain-containing adapter inducing interferon (IFN)-beta (TRIF), and TRIF-related adapter molecule (TRAM). TLR signaling consists of two distinct pathways, MyD-88-dependent and MyD-88-independent: (1) MyD-88-dependent pathway: The MyD88 dependent pathway is down-stream of TLR1, TLR2, TLR4, TLR5, TLR6, TLR7 and TLR9. This pathway leads to the production of proinflammatory cytokines and is triggered by the association of activated TIR domain and MyD-88, recruitment of IRAK1, IRAK4 and TRAF6 to the TLR-MyD-88 complex and consequent phosphorylation of IRAK1 and TRAF6. The signal is propagated by this phosphorylated adaptor molecular complex to the down-stream MAP kinases-AP1 and IKK complex-NF-κB; (2) MyD88-independent pathway: This is associated with the induction of INF-beta mediated by TLR3 or TLR4 activation. Intracellular signaling *via* the MyD-88 independent pathway is propagated by the action of TRIF and TRAM as adaptor molecules. The signal consequently activates the IKK pathway to produce INF-beta.

by TLR4[14]. A comprehensive microarray study revealed that TLR2-transfected HEK-293 cells stimulated by *H. pylori* up-regulated the expression of 28 key genes of inflammatory mediators through the TLR2 pathway[37]. Smith *et al*[38] showed that TLR2 of gastric epithelial cells initiated the Tribbles 3-NF-κB signaling pathway by stimulation of *H. pylori*-LPS. NAP has also been reported to work as a ligand of TLR2 *via* DAMP recognition[39]. Therefore, TLR2 is considered an important participant in the formation of gastric innate immunity against *H. pylori*[37-42].

COOPERATION BETWEEN TLR4 AND TLR2 IN *H. PYLORI* - INDUCED INNATE IMMUNITY

Previously, we reported that *H. pylori*-LPS was able to augment TLR2 expression through TLR4 signaling, which was propagated through the extracellular-signal-regulated kinase (ERK)-NF-κB pathway in human gastric epithelial cells[19]. TLR2 activation by *H. pylori*-LPS was also shown to enhance the expression of TLR4 *via* the MAP/ERK 1/2 kinases pathway during proliferation of gastric epithelial cells[43]. Yet, other studies have reported that TLR2 and TLR4 work in isolation. Lepper *et al*[44] demonstrated that, although *H. pylori* LPS induced an inflammatory response through TLR2, *H. pylori*-LPS from some strains possibly antagonized TLR4. Obonyo *et al*[45] showed that TLR2 induced proinflammatory cytokines, IL-1 and IL-6, in the presence of *H. pylori*, whereas TLR4 induced immune regulatory cytokines IL-10 and IL-12.

Due to differences in the study model, cell context, *H. pylori* strains, and purity of *H. pylori*-LPS, study results to date have been inconclusive regarding the responsiveness of TLR2 and TLR4 in *H. pylori*-infected gastric mucosa[46]. However, the cooperation between TLR2 and TLR4 is advantageous to enhance and establish innate and acquired immunity. In the low acidic environment of *H. pylori*-infected atrophic gastric mucosa, the interaction of TLR2 and TLR4 increases the susceptibility to a variety of *H. pylori* virulence determinants and concomitant infection with gram-positive bacteria from salivary

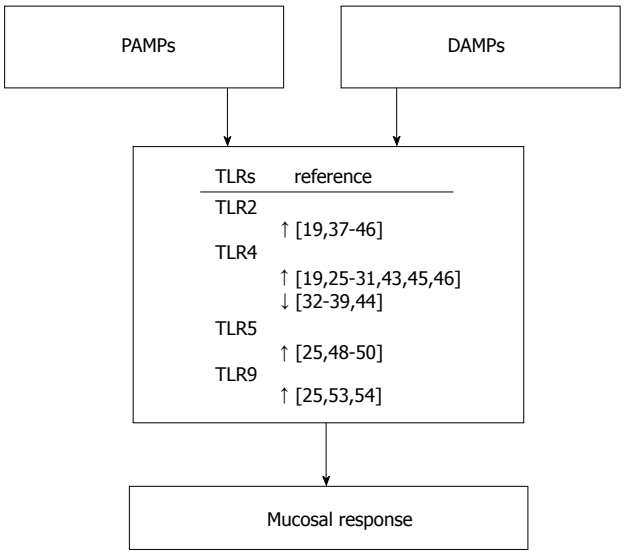

Figure 2 Role of toll-like receptors in *Helicobacter pylori* induced innate immunity. Toll-like receptors (TLRs) can sense structurally conserved molecules (pathogen-associated molecular patterns, PAMPs) as well as damage-associated molecular patterns (DAMPs) produced under stress conditions. These recognition systems direct the wide-ranging responsiveness of TLRs not only to foreign agents, but also to internal organisms denatured by inflammation.

or dietary contamination[19,47].

OTHER TLRS RELATED TO *H. PYLORI* INFECTION

In addition to TLR2 and TLR4, other TLRs are related to *H. pylori* infection. *H. pylori* possess multiple flagella. *H. pylori*-flagellin A (FlaA) is a component protein of flagella, which is recognized by flagellin receptor TLR5. In general, TLR5 signaling is known to induce IL-8 secretion *via* p38 MAP kinase signaling initiated by recognition of a bacterial flagellin[48-50]. However, some studies showed that FlaA was a very weak activator of IL-8 induction[51,52].

TLR9 has been shown to recognize *H. pylori* unmethylated CpG DNA, resulting in the production of type- I IFN[53]. Rad *et al*[54] showed that TLR9 stimulated by *H. pylori* induced proinflammatory cytokines, such as IL-6 and IL-12. Moreover, according to immunohistochemical studies, the apical and basolateral expressions of TLR5 and TLR9 identified in non-inflamed gastric epithelium dynamically acquired a basolateral distribution in *H. pylori*-infected mucosa[25,50].

RELATIONSHIPS BETWEEN TLRS AND GASTRIC CARCINOGENESIS

H. pylori was classified as a group I definite carcinogen in 1994 by the International Agency for Research on Cancer[55]. The inflammation-cancer association plays an important role in formation of the tumor microenvironment, characterized by infiltration of tumor-associated macrophages, activation of fibroblasts, epithelial cell remodeling, and angiogenesis[56]. The TLR pathways activated by *H. pylori*-induced inflammation may be implicated not only in gastric carcinogenesis, but also in formation of the tumor microenvironment through the production of pro-inflammatory cytokines, chemokines, and reactive oxygen species.

The degree of expression of TLR2, TLR4, and TLR5 gradually increases from intact gastric epithelium, to metaplasia, to dysplasia, and adenocarcinoma[49]. In addition, their localization shifts diffusely and homogeneously into the cytoplasm in gastric cancer cells, as compared to that in *H. pylori*-infected gastric mucosa[49]. In late-stage gastric carcinogenesis, their intense expressions in cancerous cells are likely to activate pro-oncogenic processes through prolonged stimulation of TLRs[57].

Recently, Tye *et al*[58] revealed that STAT3-driven up-regulation of TLR2 promoted gastric carcinogenesis using the gp130$^{F/F}$ preclinical mouse model, which would lead to gastritis and gastric cancer through activation of STAT3 even in a non-infectious condition. STAT3 signaling is initiated by the action of the IL-6 cytokine family, the production of which is facilitated by the interaction between TLR2 and *H. pylori*. As a result, TLR2 and IL-6/STAT3 signaling possibly form a positive feedback loop in *H. pylori*-infected gastric mucosa[59,60]. STAT3 was also reported to correlate with lymph node metastasis and immortality of gastric cancer cells[61]. Therefore, a TLR2/IL-6/STAT3 loop might play an important role in gastric carcinogenesis.

Other studies have shown that up-regulation of DAMPs may augment TLR4-mediated immune and non-immune signaling in the development of colitis-associated colon cancer[59]. Additional roles of DAMPs-activated TLR pathways probably contribute to gastric carcinogenesis caused by *H. pylori* infection.

GENE POLYMORPHISMS OF TLRS IN GASTRIC CARCINOGENESIS

H. pylori is a major cause of gastric cancer, but only 1%-2% of *H. pylori*-infected individuals develops gastric cancer[62]. Recently a meta-analysis of large population-based cohort studies in Europe revealed an association between a variation of TLR1 genetic loci (4p14) and *H. pylori* seroprevalence[63]. The study was conducted in White populations, therefore some sample bias should be considered in different races. However, the polymorphisms of TLRs might play an important role in modulation of the direction and magnitude of the host response against infection. This might also encourage a possible link between genetic polymorphisms of TLRs and *H. pylori*-associated carcinogenesis. Recent studies revealed the presence of single-nucleotide polymorphisms (SNPs) of TLRs and their relationships with gastric cancer development (Table 1). However, the implications of SNPs in genetic function have not been fully clarified.

The *TLR4* gene is located in chromosome 9q32-q33 and contains 4 exons. TLR4 Asp299Gly (rs4986790)

Table 1 Associations between polymorphisms in toll-like receptor genes and risk of gastric cancer

TLR	SNP	SNP number	Population	Case	Control	OR	95%CI	Genotyping	Ref.
TLR2	196 to 174 del		Chinese	69	212	1.3	0.87-1.95	Allele specific PCR	[70]
			Brazilian	200	240	2.32	1.56-3.46	Allele specific PCR	[65]
			Chinese	248	496	0.71	0.56-0.89	DHPLC	[74]
			Japanese	583	1097	1.08	0.93-1.26	PCR-CTPP	[72]
			Japanese	289	455	1.34	1.07-1.67	Allele specific PCR	[73]
TLR4	Asp299Gly	rs4986790	Brazilian	174	225	2.68	1.24-5.81	PCR-RFLP	[65]
			Chinese	60	162	0.15	0.02-1.15	PCR-RFLP	[66]
			Italian	171	151	1.05	0.46-2.37	PCR-RFLP	[67]
			Polish	312	419	2.5	1.6-4.0	PCR-RFLP	[68]
			United States	211	184	2.1	1.1-4.2	PCR-RFLP	[68]
			Mexican	78	236	1.07	0.41-2.77	PCR-RFLP	[69]
	AspThr399Il3	rs4986791	Brazilian	174	225	1.97	0.69-5.57	PCR-RFLP	[65]
			Italian	171	151	3.9	1.30-11.72	PCR-RFLP	[67]
			Mexican	78	236	0.23	0.03-1.76	PCR-RFLP	[69]
	3725 G>C	rs11536889	Chinese	68	203	1.89	1.23-2.92	Mass spectrometry	[70]
			Germany, Lithuania, Latvia	113	238	1.03	0.62-1.71	PCR-CTPP	[71]
			Japanese	583	1056	0.99	0.84-1.16	PCR-CTPP	[72]
TLR5	889 T>C	rs5744174	Chinese	248	496	1.43	1.03-1.97	DHPLC	[74]
TLR9	1486 T>C		Chinese	314	314	1.49	1.07-2.07	PCR-RFLP	[75]
	1237 T>C		Polish	312	419	0.9	0.6-1.3	PCR-RFLP	[76]
			United States	211	184	0.6	0.4-1.0	PCR-RFLP	[76]

TLRs: Toll-like receptors; PCR: Polymerase chain reaction; SNPs: Single-nucleotide polymorphisms.

and Thr399Ile (rs4986791) are located in the coding sequence in amino acid substitutions associated with the TLR4 extracellular domain[64]. TLR4 Asp299Gly polymorphism can functionally diminish the binding affinity of bacterial ligands, resulting in a diminished response to *H. pylori*-LPS. These alterations might contribute to prolonged infection, subsequent chronic inflammation, and carcinogenesis. However, there are discrepancies in the association between TLR4 Asp299Gly[65-69] or TLR4 Thr399Ile[65,67,69] polymorphism and gastric cancer incidence, *i.e.*, a Chinese case-control study showed a positive association between TLR4 3725G/C polymorphism and gastric cancer risk[70], but the association was not confirmed by Caucasian or Japanese case-control studies[71,72].

TLR2 is located in the long arm of chromosome 4 comprising two 5' non-coding exons followed by a third coding exon. A TLR2 -196 to -174del polymorphism by a 22-bp deletion can affect the promoter activity of TLR2. A Brazilian study and a Japanese study both revealed a positive relationship between TLR2 -196 to -174del polymorphism and the development of gastric cancer[69,73], but a Chinese study revealed a negative relationship[74], and another study carried out in Japan showed no significant association[72].

Neither SNPs of TLR5 (889T/C[74]) nor TLR9 (1486T/C[75], 1237T/C[75,76]) is associated with gastric cancer incidence. Studies of the association between SNPs of TLRs and gastric cancer incidence are still limited and conflicting. A recent study by de Oliveira *et al*[65] demonstrates that a combination of polymorphisms of cytokines and TLRs strongly indicates a higher risk of developing gastric cancer. Therefore, further studies are warranted to assess the pathophysiologic significance of SNPs of TLRs.

CONCLUSION

In this review, we have provided a summary of novel TLR-related research. The role of TLRs in gastric innate immune responses against *H. pylori* should be carefully interpreted with close attention to differences in study models, such as cell-contexts, strains of *H. pylori*, and ethnicity of study subjects. The role of TLRs in gastric carcinogenesis remains unclear, since there is a possibility that the dual role of TLR signaling in carcinogenesis might act as a double-edged sword, *i.e.*, tumor progression and suppression dependent on the cellular origin or the types of TLRs. However, TLR-associated innate immunity is essential in first-line defense and the initiation of acquired immunity against *H. pylori* infection. The pathophysiologic roles of TLRs in gastric cancer development, including their SNPs, remain unknown. Both PAMPs derived from *H. pylori* and DAMPs from *H. pylori*-induced inflammation may be implicated in the various processes of gastric cancer development. In future, TLR targeting therapy might provide a foresight of gastric cancer treatment. Further studies are warranted to assess the association between *H. pylori* infection and gastric cancer development.

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