PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2006 May 7; 12(17): 2713-2720
World Journal of Gastroenterology ISSN 1007-9327

REVIEW

Latest insights into the effects of *Helicobacter pylori* infection on gastric carcinogenesis

Kazunari Murakami, Masaaki Kodama, Toshio Fujioka

Kazunari Murakami, Masaaki Kodama, Toshio Fujioka, Department of Gastroenterology, Oita University Faculty of Medicine, Oita, Japan
Supported by a Grant-in Aid for Cancer Research from the Japanese Ministry of Health and Welfare, No. 08457170
Correspondence to: Kazunari Murakami, MD, Department of Gastroenterology, Oita University Faculty of Medicine, 1-1 Idaigaoka, Hasama, Oita 879-5593, Japan. murakam@med.oita-u.ac.jp
Telephone: +81-97-5866193 Fax: +81-97-5866194
Received: 2005-09-01 Accepted: 2005-10-09

Abstract

There appears to be the strong association between *Helicobacter pylori* (*H pylori*) and gastric cancer. We reviewed the latest evidences about the effects of *H pylori* infection on gastric carcinogenesis, classified into epidemiology, dynamics of gastric mucosal changes, DNA damages, virulence factors, host factors, and source of gastric malignancy. Through the considerable progress made in research into virulence factors resulting from differences between *H pylori* strains, such as *cagA* positivity, as well as into host factors, such as gene polymorphisms, a diverse spectrum of *H pylori*-associated diseases, including gastric cancer, is beginning to lend itself to elucidation. The impact of the novel hypothesis advanced by Houghton *et al* proposing bone-marrow derived stem cells (BMDC) as a potential source of gastric malignancy on evolving research remains to be seen with interest. Further progress in research into *H pylori* eradication as a viable prophylaxis of gastric cancer, as well as into the mechanisms of gastric carcinogenesis, is to be eagerly awaited for the current year and beyond.

Key words: *Helicobacter pylori*; Gastric cancer; Carcinogenesis; *CagA*; Intestinal metaplasia

Murakami K, Kodama M, Fujioka T. Latest insights into the effects of *Helicobacter pylori* infection on gastric carcinogenesis. *World J Gastroenterol* 2006; 12(17): 2713-2720

http://www.wjgnet.com/1007-9327/12/2713.asp

INTRODUCTION

By now, there appears to be no doubt about the strong association between *Helicobacter pylori* (*H pylori*) and gastric cancer, and the focus of current research interest has now shifted to the mechanism of gastric carcinogenesis associated with *H pylori* infection, long regarded as a black box, which is now beginning to be unraveled thanks to the considerable progress made in this area through the clarification of various aspects including *cagA*. Difficult as it is to cover the full spectrum of papers accumulated on *H pylori* and gastric cancer even in the last few years, in what follows, we propose to provide a review of the literature, while drawing on selected papers of interest on this topic.

EPIDEMIOLOGY

In the beginning of 2004, Wong *et al*[1] reported on the results of a randomized controlled trial investigating the association between *H pylori* eradication and prophylaxis of gastric cancer in 1630 patients with *H pylori* infection (of whom 988 patients were found to have no precancerous lesions, such as atrophy of gastric mucosa, intestinal hyperplasia, or atypical epithelium) allocated to either the eradication arm or placebo arm and followed up for 7.5 years. Of the patients who developed gastric cancer during follow-up, 7 had had *H pylori* eradicated, and 11 had received placebo, and there was no significant ($P=0.33$) difference in the incidence of gastric cancer between the two arms. However, a subset analysis of patients without precancerous lesions in both the treatment and placebo arms revealed that the incidence of gastric cancer was 6 in the placebo arm *versus* 0 in the treatment arm ($P=0.02$), suggesting that *H pylori* eradication significantly inhibited the incidence of gastric carcinogenesis in patients without precancerous lesions.

In another randomized, double-blind, placebo-controlled trial in 248 patients, of whom 122 received eradication, and 126 received placebo, Ley *et al*[2] reported in their follow-up ranging from 6 wk to 1 year that there was no significant improvement with *H pylori* eradication in the consensus "worst biopsy" diagnosis, while there was improvement in the weighted index score, and concluded that the study results do not prove that eradication of *H pylori* decreases cancer risk. However, these inconclusive

results may be attributable to the short-term follow-up of the study.

The Japan Collaborative Cohort (JACC) Study Group for Evaluation of Cancer Risk reported that women with a family history of gastric cancer and infected with *H pylori* were associated with a 5.10-fold risk for gastric cancer compared to women without a family history of gastric cancer and *H pylori* infection[3]. In contrast, family history and *H pylori* infection were not found to be significant risk factors for gastric cancer in male patients in their report, where the investigations of *H pylori* infection were performed using only *H pylori* antibodies.

Matsuhisa *et al*[4] investigated the ratio of corpus gastritis to antrum gastritis (C/A ratio) in *H pylori*-positive Chinese, Thai and Vietnamese adult populations compared to the Japanese population by evaluating the degree of neutrophil activity in the corpus and antrum of these patients. The C/A ratio was found to be significantly higher in the Japanese population compared to the other populations, where corpus-predominant gastritis was characteristic of aged Japanese and Chinese (Fuzhou), while, in contrast, gastritis in Chinese (Beijing), Thai and Vietnamese was found to be antrum-predominant, which is considered to be related to the low incidence of gastric cancer in Thai and Vietnamese.

Brenner *et al*[5] demonstrated in a case-control study that after excluding those who met the exclusion criteria (blood sample taken more than 90 d after gastrectomy, advanced (T4) gastric cancer, and *cagA* positivity in Western blot analysis despite a negative result in anti-*H pylori* immunoglobulin G enzyme-linked immunosorbent assay), as well as those who had borderline levels in immunoglobulin G enzyme-linked immunosorbent assay, the odds ratio for noncardia gastric cancer was increased from 3.7 to 18.3 in those with any *H pylori* infection, and from 5.7 to 28.4 in those with *cagA*-positive *H pylori* infection. The authors therefore concluded that *H pylori* infection might even be a (close to) necessary condition for the development of nocardia gastric cancer.

In a multi-center trial evaluating 2 503 patients with histologically confirmed gastric cancer *versus* 6 578 control subjects, Kato *et al*[6] demonstrated that *H pylori* infection was strongly associated with the development of gastric cancer ($OR = 2.47$), while there were no significant differences in the prevalence of *H pylori* infection, histological subtypes of gastric cancer (intestinal type *vs* diffuse type), or sites of gastric cancer occurrence (antrum, corpus and cardia) between the gastric cancer and control subjects.

Shiotani *et al*[7] demonstrated that *H pylori*-positive patients with pruritic skin diseases may be at increased risk for the development of gastric cancer. Leung *et al*[8] reported the results of a randomized trial on *H pylori* eradication, demonstrating that *H pylori* infection ($OR = 2.13$), 45 years of age or greater ($OR = 1.92$), alcohol intake ($OR = 1.67$) and drinking water from a well ($OR = 1.74$) are risk factors that predict the progression of intestinal metaplasia as precancerous lesions.

Camargo *et al*[9] investigated the prevalence and the age of acquisition of *H pylori* infection in children aged 1 to 8 years old residing in Pasto, Colombia, which is associated with a high prevalence of gastric cancer as compared to those in children living in Tumaco, Colombia. They found that there were no significant differences between children in Pasto and Tumaco in the prevalence and age of acquisition of *H pylori* infection, suggesting that the risk for gastric cancer is associated with the bacterial virulence of the *H pylori* strains involved.

DYNAMICS OF GASTRIC MUCOSAL CHANGES

Kato *et al*[10] investigated the sex differences in mucosal response to *H pylori* infection and found that atrophy and intestinal metaplasia scores in the corpus with *H pylori* infection were more severe in men than in women, particularly in elderly patients. They also reported that while there were no differences between the sexes with regard to interleukin-8 mRNA induction, cyclooxygenase-2 (COX-2) mRNA expression was higher in men than that in women, concluding that these differences in response between men and women may account for the 2-fold difference in the incidence of gastric cancer between the sexes.

Shiotani *et al*[11] demonstrated that the gastric nitrate and pH levels were progressively increased from patients with histological normal diagnosis to those with antral-predominant gastritis to those with pangastritis, and then on to those with corpus-predominant gastritis, suggesting that the gastric pH level is one of the prognostic markers for corpus-dominant gastritis and probably for patients at high risk of developing gastric cancer.

Of the reports that addressed post-eradication changes in the mucosa, a study by Fichman *et al*[12] demonstrated that there was improvement in acute and chronic inflammation scores, the number of lymphoid follicles, as well as an increase in the number of gastric glands, while there was no change in intestinal metaplasia over time, during a mean follow-up of 23.15 mo after *H pylori* eradication in 89 patients. They further demonstrated that the Ki67 labeling index significantly decreased after eradication, while the MUC5AC and MUC6 expressions increased. Of the numerous reports published on post-eradication changes in the gastric mucosa, many reported improvement of intestinal metaplasia with eradication of *H pylori*, suggesting the potential role of *H pylori* eradication in the prophylaxis of gastric carcinogenesis[13-15].

Iijima *et al*[16] also reported that *H pylori* infection showed a stronger inhibitory effect on acid secretion in males than that in females. Ohata *et al*[17] demonstrated in a longitudinal cohort study in 4 655 healthy subjects with a mean follow-up of 7.7 years that 45 subjects subsequently developed gastric cancer. In this study, *H pylori* infection was established by serum-specific antibodies and the presence of chronic atrophic gastritis was confirmed by measurement of serum pepsinogen I and II. They also demonstrated that *H pylori* infection and gastric mucosal atrophy were both strongly implicated in gastric carcinogenesis and that *H pylori*-negative patients in whom there was no evidence of gastric atrophy did not develop

gastric cancer. Furthermore, they concluded that while *H pylori* infection is not directly associated with gastric carcinogenesis, it is indirectly implicated in it by promoting gastric atrophy, and severe gastritis with extensive intestinal metaplasia is a major risk factor for gastric cancer.

Suzuki *et al*[18] provided evidence that *H pylori* eradication exerted an inhibitory effect on the proliferation of epithelial cells as shown by the tissue content of hepatocyte growth factor (HGF) and Ki67 labeling index. Our previous study also demonstrated that *H pylori* eradication led to a decrease in the expressions of *p53* and multiple double minute 2 (MDM2) in the epithelial cells, which had been elevated prior to eradication[19] .

DNA DAMAGE

Ladeira *et al*[20], using the comet assay or single-cell gel electrophoresis, investigated the status of DNA damage in gastric epithelial cells from the antrum and corpus in *H pylori*-infected patients with gastritis of varying degrees, and demonstrated that the level of DNA damage in *H pylori*-infected individuals was significantly higher (8.4-fold) than that in non-infected individuals, with the levels of DNA damage significantly higher in those aged 50 years or more.

The DNA repair enzyme human oxoguanine glycosylase 1 (hOGG1) is known to be responsible for the repair of the 8-hydroxy-deoxyguanosine (8-OHdG) region. Of the hOGG1 polymorphisms identified, a Ser→ Cys polymorphism at position 326 was found to interact with atrophic gastritis, but not with antioxidant dietary or nutrient intakes, likely making patients with atrophic gastritis who also have the hOGG1 Cys allele more susceptible to gastric cancer[21] .

The concentrations of 8-OHdG, inducible nitric oxidative synthase (iNOS), nuclear factor κB (NF-κB), myeloid cell leukemia-1 (Mcl-1) and inhibitor of apoptosis protein (IAP) were reported to be significantly higher in patients with *H pylori* infection, in cancer tissues, and in stage 3 and 4 gastric cancer patients, pointing to the pivotal role that oxygen-free radical-mediated DNA damage due to *H pylori* infection plays in the development of gastric carcinoma from chronic gastritis[22].

VIRULENCE FACTORS

CagA proteins and gastric carcinoma

H pylori virulence factors include the cytotoxin-associated gene A antigen (CagA), the vacuolating cytotoxin (VacA), urease, and blood group antigen-binding adhesin (BabA). After the year 2000, much has been clarified about the behavior of CagA proteins, where *H pylori* could directly deliver the CagA protein into the host epithelial cell cytoplasm via the *cag* PAI-coded type IV export system[23]. Inside the epithelial cells, the CagA protein undergoes tyrosine phosphorylation by the host Src family protein tyrosine kinases, and the CagA protein binds an Src homology 2 (SH-2) domain-containing tyrosine phosphatase SHP-2, and stimulates the division and proliferation of gastric epithelial cells[24] .

Twenty percent of the tyrosine-phosphorylated CagA also binds carboxyl-terminal Src kinase (Csk) with 80% of the tyrosine-phosphorylated CagA binding SHP-2. The CagA-Csk interaction activates Csk and inactivates the Src family kinases, thereby bringing about a decrease in CagA tyrosine-phosphorylation as well as in CagA-SHP2 interactions as a feedback mechanism[25]. Through this mechanism, chronic infection with *cagA*-positive strains persists, thus causing the host damage.

There are two subtypes of the CagA proteins reported, namely the Western CagA and East Asian CagA[26] . Due to the presence of polymorphisms in tyrosine phosphorylation sites, the East Asian CagA proteins were reported to have a significantly higher SHP-2-binding affinity than the Western CagA proteins, whereas the Western CagA proteins with repeated EPIYA motifs are associated with greater CagA phosphorylation, and higher SHP-2-binding affinity, and greater induction of the hummingbird phenotype than the Western CagA proteins without repeated EPIYA motifs[26]. However, the East Asian CagA proteins, with a different amino acid sequence downstream of the third EPIYA motif, are reported to exhibit even greater activity than the potent Western CagA proteins.

Argent *et al*[27] also reported that the more EPIYA motifs present in the CagA proteins, the higher the degree of CagA tyrosine-phosphorylation and the level of CagA biologic activity in inducing human gastric epithelial (AGS) cell elongation (hummingbird phenotype), and the more likely they are to be associated with gastric cancer.

In the host cell, the tyrosine-phosphorylated CagA protein induces rearrangements of the actin cytoskeleton. The tyrosine-phosphosphorylated CagA inhibits the catalytic activity of Src family kinases and induces tyrosine-dephosphorylation of several host cell proteins, one of which has been identified as ezrin. Ezrin is a component of microvilli, and makes up the ezrin-radixin-moesin (ERM) family of proteins as a linker protein between actin filaments and membrane proteins, and thus is deemed responsible for the adhesion and division of molecules as well as for intracellular signaling. This suggests that ezrin dephosphorylation may be implicated in the mechanism of gastric carcinogenesis[28].

Given the well known fact that the incidence of gastric cancer in Okinawa Prefecture, Japan is quite low, Azuma *et al*[29] compared the *H pylori* strains prevalent in Fukui and Okinawa Prefectures, and found that, of the strains examined, those found in Fukui were all of the East Asian CagA subtype; and, of the 42 strains associated with gastritis in Okinawa, 6 strains (14.3%) were *cagA*-negative, 8 strains (19.0%) were of the Western CagA subtype, and 28 strains (66.7%) were of the East Asian CagA subtype; and all strains associated with gastric carcinoma were of the East Asian CagA subtype. The degree of inflammation, activity of gastritis, and gastric mucosal atrophy observed in the East Asian *cagA*-positive strains were significantly more advanced than that in the Western *cagA*-positive or -negative strains, suggesting that infection with East Asia *cagA*-positive *H pylori* strains is strongly associated with gastric atrophy and cancer.

Furthermore, Azuma *et al*[30] compared the distribution of CagA polymorphisms in the world and analyzed the

relationship between the CagA distribution and associated mortality rate of gastric cancer. In this report, they noted that no East Asian CagA proteins were found in the West, while all CagA proteins reported in Asia were of the East Asian CagA subtype, with the prevalence of the East Asian CagA subtype found to be correlated well with the mortality rate from gastric cancer, thus concluding that searching for CagA polymorphisms rather than mere *H pylori* infection may be of greater value in identifying patients at increased risk of developing gastric cancer.

Azuma *et al*[31] also reported on several genes in a pathogenicity island (PAI) known as *cag* PAI, of which the *cagA* gene is one. According to their report, the *cag* PAI can be classified by their polymorphisms into the Japanese and Western clusters, and their diversity is associated with the *vacA* and *cagA* genotypes; and all strains with the *s1c vaA* genotype as well as with the East Asian *cagA* genotype are found in the Japanese cluster. They also noted that patients infected with strains found in the Japanese cluster were associated with high grade gastric mucosal atrophy and that while nearly all patients with *H pylori* infection are found to be *cag* PAI-positive, of all *cag* PAI polymorphisms, the Japanese cluster-genotypes appear to be predominantly associated with advanced gastric atrophy and increased gastric cancer risk.

Kauser *et al*[32] investigated the chromosomal integrity or lack of the *cag* PAI across different populations by evaluating the biogeographical distribution of strains carrying the fully integral *cag* PAI. According to their report, the *cag* PAI was well conserved in the East Asian clinical isolates and most highly conserved in the Japanese clinical isolates, but least conserved in the majority of the European and African clinical isolates. They also found that the *cagE* and *cagT* genes were less often rearranged (18%) compared to the *cagA* gene, and the differing *cag* PAI rearrangement patterns were related to varying disease outcomes, with the *cagA* promoter and the left end of the *cag* PAI frequently rearranged or deleted in clinical isolates associated with severe pathology.

AI-Marhoon *et al*[33] proposed a model on the association between *cagA*-positive *H pylori* infection and distal gastric cancer, explaining how *cagA*-positive *H pylori* infection is associated with greater PGE_2 production, increased mucus thickness and hydrophobicity, which serve to protect and keep intact bacterial colonization and increase gastritis, and is therefore associated with the risk of distal gastric cancer.

Ladeira *et al*[34] showed that *cagA*, *vacA*, and *iceA* genotypes were associated with significant DNA damage in both the gastric antrum and corpus, indicating that they may serve as biomarkers for the risk of extensive DNA damage and possibly for gastric cancer.

Toward the end of 2003, Huang *et al*[35] performed a meta-analysis of the relationship between *cagA* seropositivity and gastric cancer in a total of 2284 patients with gastric cancer *versus* 2770 control subjects, demonstrating that *H pylori* infection and *cagA* positivity increased the risk for gastric cancer by 2.28-fold and 2.87-fold, respectively. They also reported that among *H pylori*-positive patients, *cagA* positivity further increased the risk for gastric cancer by 1.64-fold, and that for non-cardia gastric cancer by 2.01-fold, whereas the gastric cancer at the cardia was not associated with *H pylori* infection or *cagA* positivity, thereby concluding that *cagA* positivity is associated with a greater risk of developing gastric cancer than *H pylori* infection. Furthermore, Held *et al*[36] investigated the association between *cagA*-positive *versus cagA*-negative status and gastric cancer in a case-control study and found that *H pylori* antibody positivity was associated with a greater risk of gastric cancer than *H pylori* antibody negativity, and that cag*A* antibody positivity further increased the risk, while cag*A* antibody-negative *H pylori* infection was associated with a significantly greater risk for gastric cancer than *cagA* antibody- and *H pylori* antibody-negative status.

There are several reports, however, that tend to negate the role of *cagA* as a risk factor for gastric cancer, while acknowledging its importance. Hirata *et al*[37] reported on the functional variability of the *cagA* gene in 36 clinical strains isolated from Japanese patients with various gastric diseases. They demonstrated that while delivery of the CagA protein into the host epithelial cell cytoplasm in the majority of Japanese patients with *H pylori* infection is ensured via the type IV export system, and tyrosine-phosphorylation of the CagA protein is promoted, the intensity of CagA phosphorylation as well as the activation of the serum response element (SRE) vary greatly among the *cagA*-positive strains, with those associated with gastric cancer, MALToma and chronic atrophic gastritis found to be slightly higher than those associated with gastroduodenal ulcers. They also noted that while the *cagA* polymophisms and the number of EPIYA motifs repeated should account in part for the variety of resulting diseases, the association between *cagA* status and disease outcome might not be too strong.

Bachert *et al*[38] performed a functional analysis of the *cag* PAI in 25 *H pylori* strains each isolated from patients with gastritis, peptic ulcer disease, and gastric cancer, and demonstrated that *cagA* expression, translocation and tyrosine-phosphorylation were high but similar among all patient groups examined, suggesting that while the *cag* PAI-dependent processes remain an important *H pylori*-associated virulence factor, the determination of disease outcome may be highly complex and involve multiple bacterial and/or host factors. Similarly, Nishiya *et al*[39] investigated the role of the *cag* PAI by performing an analysis of 39 *H pylori* strains each isolated from Japanese patients with gastric cancer and chronic gastritis, respectively, where the presence of *cagA*, *cagE*, and *VirD4* homologue was studied. They reported that almost all patients were found to be *cagA*-positive, and there were no differences between patients with gastric cancer and chronic gastritis with regard to the expression of *cagA*, *cagE* and *VirD4*, thus concluding that the structure of the *cag* PAI might not be associated with the development of gastric cancer in Japanese patients.

Apart from this, while the interaction between *H pylori* infection and gastroesophageal reflux disease (GERD) has long been under debate, Ye *et al*[40] showed in a large population-based case-control study in Sweden that *H pylori* infection might prevent the development of GERD and reduce the risk of esophageal adenocarcinoma,

whereas gastric atrophy and infection with *cagA*-positive stains of *H pylori* might increase the risk for esophageal squamous cell carcinoma.

OTHER VIRULENCE FACTORS

In an analysis of gene expression profiles using gastric cancer cells, Yuan *et al*[41] reported that VacA affects cytoskeleton-associated genes, thereby disrupting cytoskeletal architecture; it also causes damage to cell cycle-related genes, and breaks the balance between cell proliferation and cell death, while at the same time inducing inflammatory responses.

In a comparison of the *hrgA* gene thought to encode a restriction enzyme in *H pylori* using clinical isolates from East Asian and Western countries, the prevalence of *hrgA*-positive strains was reported to be significantly higher in the Western countries (49%) compared to the East Asian countries (20%). However, the prevalence of the *hrgA* gene was not found to be related to disease specificity or to other important putative virulence factors (*i.e.,* CagA, VacA)[42].

Gastric mucosal interleukin 8 (IL-8) levels are related to the presence of both the *cag* PAI and the outer inflammatory protein (OipA)[43]. Yamaoka *et al*[44] examined the upstream IL-8 signal transduction pathway including the *H pylori*-associated IL-8 promoter and gene transcription region using *oipA*, *hepZ*, *cagE* gene knockout cultured cells. Maximization of *H pylori*-induced IL-8 gene transcription requires the presence of binding sites for ISRE-like element, NF-κB, and AP-1. Both the OipA and *cag* PAI are implicated in the process in which the interferon regulatory factor (IRF)-1 becomes activated by binding the interferon-stimulated responsive element (ISR)-like element, while the *cag* PAI, and not the OipA, is implicated in the activation of AP-1 and NF-κB. Again, the OipA, and not the *cag* PAI, is implicated *in vitro* and *in vivo* in the phophorylation of signal transducers and activators of transcription 1 (STAT1) as an upstream signal transduction pathway. Thus, while both the OipA and *cag* PAI are required for the full activation of the IL-8 promoter region, each acts via a different pathway that becomes distinct upstream of the IRF-1, with only the OipA implicated in the STAT1-IRF1-ISRE pathway. Gastric mucosal inflammatory processes are complex and involve different pathways centered on the IL-8 promoter region.

HOST FACTORS

In an experiment using gastric epithelial (AGS) cells, *H pylori* infection was found to increase the expression of plasminogen activator inhibitor (PAI)-2, suggesting that PAI-2 may play a role in influencing the progression to gastric cancer[45].

Nardone *et al*[46] demonstrated that in patients with up-regulation of COX-2 or microsomal PGE-synthase 1 (mPGES1) expressions by *H pylori* infection, the expressions of the anti-apoptosis marker *Bcl-x1* or the multi-drug resistance 1 gene (*MDR-1*) product P-gp were also increased, suggesting that this *H pylori*-induced process may contribute to gastric carcinogenesis and resistance to therapy.

It is reported that *H pylori* infection increases the mRNA expression of the apoptosis-regulating proteins Bid, Bax and Bcl-2[47], and that the tumor suppressor protein Bax translocates to the mitochondaria which subsequently undergoes fragmentation[48], suggesting that a loss of control over these apoptosis-regulating genes potentially leads to gastric carcinogenesis. Of note, these genes were found to be more markedly expressed in *cagA*-positive *H pylori* strains[47].

Of the IL-10 gene polymorphisms identified, the IL-10-1082G/-819C/-592C alleles (GCC haplotype) are reported to be associated with the highest mucosal IL-10 mRNA expression, and carriers of the GCC haplotype are associated with colonization by more virulent *cagA*, *vacAs1*, and *babA2*-positive *H pylori* strains[49], suggesting that cytokine gene polymorphisms may be implicated in the development of gastritis and gastric cancer.

The pro-inflammatory cytokine IL-1 is implicated in host susceptibility to *H pylori*-associated diseases, and recent studies have further suggested that this susceptibility may be under genetic control. Hartland *et al*[50] prospectively investigated the relationship between selected polymorphisms in three of the major IL-1 gene clusters for association with *H pylori* infection and/or gastric cancer, and reported a significant difference in the genotype frequencies for the *IL1R1 HinfI* SNP in those with current or previous evidence of *H pylori* infection as compared with those without (GG, 53% *vs* 75%; GA, 40% *vs* 19%; AA, 7% *vs* 6%; $P=0.0079$). They concluded that the relationship among IL-1 gene polymorphisms, *H pylori* and disease outcome is more complicated than previously proposed, and may not be associated with the development of gastric cancer. Polymorphisms of the IL-1 gene cluster (IL-1A, -B, and -RN) have been associated with advanced gastric cancer. In early-stage gastric cancer, Glas *et al*[51] investigated the role of host genetic susceptibility and concluded that the genotype *IL-1 RN*2/2* is associated with early-stage gastric cancer, where, in contrast to advanced disease, further pro-inflammatory cytokine polymorphisms are not implicated independently, but may act in combination to play a role in early stages of gastric carcinogenesis, while the role of *H pylori* infection in this process remains unclear. In addition, Chen *et al*[52] demonstrated in a case-control study of 142 gastric cancer patients and 164 control subjects that the carriage of *IL-1RN*2*, male gender, old age, and *H pylori* infection were associated with increased risk for gastric cancer, concluding that *H pylori* infection and *IL-1RN*2* are independent risk factors for gastric cancer, and *H pylori* testing and host genotyping may combine to help target the eradication of *H pylori* to high risk individuals.

Basak *et al*[53] investigated the role of *H pylori* lipopolysaccharide (LPS) in IL-1β gene expression and the signaling pathways leading to LPS-induced IL-1β secretion, and demonstrated that activation of the mitogen-activated protein (MAP) by LPS resulted in activation of the immediate downstream C/EBP β and the C/EBPβ-binding elements of the IL-1 promoter, thus leading to the expression of the IL-1β. Of note, they also reported that

LAP-induced activation of the Rac1/PAK1 signaling plays a role in activation of caspase-1 required for maturation of the pro-IL-1β.

Osawa *et al*[54] investigated the effect of *H pylori* infection on ghrelin, a novel peptide expressed in the gastrointestinal tract conferring potent protection against gastric mucosal inflammation[55], in 110 *H pylori*-positive and 50 *H pylori*-negative patients, and demonstrated that impaired gastric ghrelin production associated with atrophic gastritis induced by *H pylori* infection accounts for the decrease in plasma ghrelin concentration.

SOURCE OF GASTRIC MALIGNANCY

It is well accepted that epithelial cancer originates from transformation of tissue stem cells. However, this view was recently challenged by Houghton *et al*[56] in 2004, who proposed a new intriguing theory regarding gastric carcinogenesis. In their theory, it is advanced that bone marrow-derived cells (BMDC) may represent a potential source of malignancy, while they are usually recruited to sites of tissue injury and inflammation. In their experiments, C57BL/6 female mice were infected with *Helicobacter felis*, irradiated, and transplanted with galactosidase- and green fluorescent protein (GFP)-labeled bone marrow cells from male mice. At wk 20, the level of apoptosis was elevated in the infected mice, and galactosidase- and GFP-positive glands appeared. After 1 year of infection, these mice developed gastric carcinoma *in situ* or gastrointestinal intraepithelial neoplasms (GIN), which were found to be galactosidase- and GFP-positive. Houghton *et al*[56] noted that while acute injury or inflammation does not lead to a recruitment of BMDC, chronic infection of C57BL/6 mice with *Helicobacter* induces a repopulation of the stomach with BMDC, and these cells progress through metaplasia and dysplasia to intraepithelial cancer. This new hypothesis appears to have far-reaching implications for future research in gastric carcinogenesis.

H PYLORI ERADICATION AND GASTRIC CANCER

In the current review, we have addressed issues surrounding *H pylori* infection and gastric carcinogenesis. Not only long-term morphological but also genetic studies will be required to clarify whether or not improvement in gastric atrophy and intestinal metaplasia after *H pylori* eradication would lead to prophylaxis of gastric cancer or when would be the "point of no return" for such prophylaxis in the course of patient follow-up. Further long-term research into the morphological changes associated with *H pylori* eradication is also required to explore strategies for the prevention of gastric cancer with *H pylori* eradication.

REFERENCES

1 **Wong BC,** Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, Lai KC, Hu WH, Yuen ST, Leung SY, Fong DY, Ho J, Ching CK, Chen JS. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004; **291**: 187-194

2 **Ley C**, Mohar A, Guarner J, Herrera-Goepfert R, Figueroa LS, Halperin D, Johnstone I, Parsonnet J. *Helicobacter pylori* eradication and gastric preneoplastic conditions: a randomized, double-blind, placebo-controlled trial. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 4-10

3 **Yatsuya H,** Toyoshima H, Tamakoshi A, Kikuchi S, Tamakoshi K, Kondo T, Mizoue T, Tokui N, Hoshiyama Y, Sakata K, Hayakawa N, Yoshimura T. Individual and joint impact of family history and *Helicobacter pylori* infection on the risk of stomach cancer: a nested case-control study. *Br J Cancer* 2004; **91**: 929-934

4 **Matsuhisa T**, Matsukura N, Yamada N. Topography of chronic active gastritis in *Helicobacter pylori*-positive Asian populations: age-, gender-, and endoscopic diagnosis-matched study. *J Gastroenterol* 2004; **39**: 324-328

5 **Brenner H**, Arndt V, Stegmaier C, Ziegler H, Rothenbacher D. Is *Helicobacter pylori* infection a necessary condition for noncardia gastric cancer? *Am J Epidemiol* 2004; **159**: 252-258

6 **Kato M,** Asaka M, Shimizu Y, Nobuta A, Takeda H, Sugiyama T. Relationship between *Helicobacter pylori* infection and the prevalence, site and histological type of gastric cancer. *Aliment Pharmacol Ther* 2004; **20 Suppl 1**: 85-89

7 **Shiotani A,** Sakurane M, Furukawa F. *Helicobacter pylori*-positive patients with pruritic skin diseases are at increased risk for gastric cancer. *Aliment Pharmacol Ther* 2004; **20 Suppl 1**: 80-84

8 **Leung WK**, Lin SR, Ching JY, To KF, Ng EK, Chan FK, Lau JY, Sung JJ. Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on *Helicobacter pylori* eradication. *Gut* 2004; **53**: 1244-1249

9 **Camargo MC**, Yepez MC, Ceron C, Guerrero N, Bravo LE, Correa P, Fontham ET. Age at acquisition of *Helicobacter pylori* infection: comparison of two areas with contrasting risk of gastric cancer. *Helicobacter* 2004; **9**: 262-270

10 **Kato S**, Matsukura N, Togashi A, Masuda G, Matsuda N, Yamada N, Naito Z, Matsuhisa T, Tajiri T. Sex differences in mucosal response to *Helicobacter pylori* infection in the stomach and variations in interleukin-8, COX-2 and trefoil factor family 1 gene expression. *Aliment Pharmacol Ther* 2004; **20 Suppl 1**: 17-24

11 **Shiotani A,** Iishi H, Kumamoto M, Nakae Y. *Helicobacter pylori* infection and increased nitrite synthesis in the stomach. Inflammation and atrophy connections. *Dig Liver Dis* 2004; **36**: 327-332

12 **Fichman S**, Niv Y. Histological changes in the gastric mucosa after *Helicobacter pylori* eradication. *Eur J Gastroenterol Hepatol* 2004; **16**: 1183-1188

13 **Ohkusa T**, Fujiki K, Takashimizu I, Kumagai J, Tanizawa T, Eishi Y, Yokoyama T, Watanabe M. Improvement in atrophic gastritis and intestinal metaplasia in patients in whom *Helicobacter pylori* was eradicated. *Ann Intern Med* 2001; **134**: 380-386

14 **Ito M,** Haruma K, Kamada T, Mihara M, Kim S, Kitadai Y, Sumii M, Tanaka S, Yoshihara M, Chayama K. *Helicobacter pylori* eradication therapy improves atrophic gastritis and intestinal metaplasia: a 5-year prospective study of patients with atrophic gastritis. *Aliment Pharmacol Ther* 2002; **16**: 1449-1456

15 **Watanabe H**, Yamaguchi N, Kuwayama H, Sekine C, Uemura N, Kaise M, Nakamura T, Kubo M, Yoshida S, Haruma K, Inoue M, Shimatani T, Sanuki E, Mieno H, Kawanishi M, Nakazawa S, Tanaka T. Improvement in gastric histology following *Helicobacter pylori* eradication therapy in Japanese peptic ulcer patients. *J Int Med Res* 2003; **31:** 362-369

16 **Iijima K,** Ohara S, Koike T, Sekine H, Shimosegawa T. Gastric acid secretion of normal Japanese subjects in relation to *Helicobacter pylori* infection, aging, and gender. *Scand J Gastroenterol* 2004; **39:** 709-716

17 **Ohata H**, Kitauchi S, Yoshimura N, Mugitani K, Iwane M, Nakamura H, Yoshikawa A, Yanaoka K, Arii K, Tamai H, Shimizu Y, Takeshita T, Mohara O, Ichinose M. Progression of chronic atrophic gastritis associated with *Helicobacter pylori* infection increases risk of gastric cancer. *Int J Cancer* 2004; **109**:

138-143
18 **Suzuki M**, Suzuki H, Masaoka T, Tanaka S, Suzuki K, Ishii H. *Helicobacter pylori* eradication treatment modulates epithelial cell proliferation and tissue content of hepatocyte growth factor in the gastric mucosa. *Aliment Pharmacol Ther* 2004; **20** Suppl 1: 158-164
19 **Kodama M,** Fujioka T, Murakami K, Okimoto T, Sato R, Watanabe K, Nasu M. Eradication of *Helicobacter pylori* reduced the immunohistochemical detection of p53 and MDM2 in gastric mucosa. *J Gastroenterol Hepatol* 2005; **20**: 941-946
20 **Ladeira MS**, Rodrigues MA, Salvadori DM, Queiroz DM, Freire-Maia DV. DNA damage in patients infected by Helicobacter pylori. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 631-637
21 **Tsukino H**, Hanaoka T, Otani T, Iwasaki M, Kobayashi M, Hara M, Natsukawa S, Shaura K, Koizumi Y, Kasuga Y, Tsugane S. hOGG1 Ser326Cys polymorphism, interaction with environmental exposures, and gastric cancer risk in Japanese populations. *Cancer Sci* 2004; **95**: 977-983
22 **Chang CS**, Chen WN, Lin HH, Wu CC, Wang CJ. Increased oxidative DNA damage, inducible nitric oxide synthase, nuclear factor kappaB expression and enhanced antiapoptosis-related proteins in *Helicobacter pylori*-infected non-cardiac gastric adenocarcinoma. *World J Gastroenterol* 2004; **10**: 2232-2240
23 **Asahi M**, Azuma T, Ito S, Ito Y, Suto H, Nagai Y, Tsubokawa M, Tohyama Y, Maeda S, Omata M, Suzuki T, Sasakawa C. *Helicobacter pylori* CagA protein can be tyrosine phosphorylated in gastric epithelial cells. *J Exp Med* 2000; **191**: 593-602
24 **Higashi H**, Tsutsumi R, Muto S, Sugiyama T, Azuma T, Asaka M, Hatakeyama M. SHP-2 tyrosine phosphatase as an intracellular target of *Helicobacter pylori* CagA protein. *Science* 2002; **295**: 683-686
25 **Tsutsumi R**, Higashi H, Higuchi M, Okada M, Hatakeyama M. Attenuation of *Helicobacter pylori* CagA x SHP-2 signaling by interaction between CagA and C-terminal Src kinase. *J Biol Chem* 2003; **278**: 3664-3670
26 **Higashi H**, Tsutsumi R, Fujita A, Yamazaki S, Asaka M, Azuma T, Hatakeyama M. Biological activity of the *Helicobacter pylori* virulence factor CagA is determined by variation in the tyrosine phosphorylation sites. *Proc Natl Acad Sci U S A* 2002; **99**: 14428-14433
27 **Argent RH**, Kidd M, Owen RJ, Thomas RJ, Limb MC, Atherton JC. Determinants and consequences of different levels of CagA phosphorylation for clinical isolates of *Helicobacter pylori*. *Gastroenterology* 2004; **127**: 514-523
28 **Selbach M**, Moese S, Backert S, Jungblut PR, Meyer TF. The *Helicobacter pylori* CagA protein induces tyrosine dephosphorylation of ezrin. Proteomics 2004; **4**: 2961-2968
29 **Azuma T,** Yamazaki S, Yamakawa A, Ohtani M, Muramatsu A, Suto H, Ito Y, Dojo M, Yamazaki Y, Kuriyama M, Keida Y, Higashi H, Hatakeyama M. Association between diversity in the Src homology 2 domain--containing tyrosine phosphatase binding site of *Helicobacter pylori* CagA protein and gastric atrophy and cancer. *J Infect Dis* 2004; **189**: 820-827
30 **Azuma T,** Ohtani M, Yamazaki Y, Higashi H, Hatakeyama M. Meta-analysis of the relationship between CagA seropositivity and gastric cancer. *Gastroenterology* 2004; **126**: 1926-1927; author reply 1927-1928
31 **Azuma T**, Yamakawa A, Yamazaki S, Ohtani M, Ito Y, Muramatsu A, Suto H, Yamazaki Y, Keida Y, Higashi H, Hatakeyama M. Distinct diversity of the cag pathogenicity island among *Helicobacter pylori* strains in Japan. *J Clin Microbiol* 2004; **42**: 2508-2517
32 **Kauser F**, Khan AA, Hussain MA, Carroll IM, Ahmad N, Tiwari S, Shouche Y, Das B, Alam M, Ali SM, Habibullah CM, Sierra R, Megraud F, Sechi LA, Ahmed N. The cag pathogenicity island of *Helicobacter pylori* is disrupted in the majority of patient isolates from different human populations. *J Clin Microbiol* 2004; **42**: 5302-5308
33 **Al-Marhoon MS**, Nunn S, Soames RW. The association between cagA+ *H pylori* infection and distal gastric cancer: a proposed model. *Dig Dis Sci* 2004; **49**: 1116-1122
34 **Ladeira MS**, Rodrigues MA, Salvadori DM, Neto PP, Achilles P, Lerco MM, Rodrigues PA, Goncalves I Jr, Queiroz DM, Freire-Maia DV. Relationships between cagA, vacA, and iceA genotypes of *Helicobacter pylori* and DNA damage in the gastric mucosa. *Environ Mol Mutagen* 2004; **44**: 91-98
35 **Huang JQ**, Zheng GF, Sumanac K, Irvine EJ, Hunt RH. Meta-analysis of the relationship between cagA seropositivity and gastric cancer. *Gastroenterology* 2003; **125**: 1636-1644
36 **Held M,** Engstrand L, Hansson LE, Bergstrom R, Wadstrom T, Nyren O. Is the association between *Helicobacter pylori* and gastric cancer confined to CagA-positive strains? *Helicobacter* 2004; **9**: 271-277
37 **Hirata Y**, Yanai A, Shibata W, Mitsuno Y, Maeda S, Ogura K, Yoshida H, Kawabe T, Omata M. Functional variability of cagA gene in Japanese isolates of *Helicobacter pylori*. *Gene* 2004; **343**: 165-172
38 **Backert S**, Schwarz T, Miehlke S, Kirsch C, Sommer C, Kwok T, Gerhard M, Goebel UB, Lehn N, Koenig W, Meyer TF. Functional analysis of the cag pathogenicity island in *Helicobacter pylori* isolates from patients with gastritis, peptic ulcer, and gastric cancer. *Infect Immun* 2004; **72**: 1043-1056
39 **Nishiya D**, Shimoyama T, Yoshimura T, Tanaka M, Fukuda S, Munakata A. Genes inside the cagPAI of *Helicobacter pylori* are not associated with gastric cancer in Japan. *Hepatogastroenterology* 2004; **51**: 891-894
40 **Ye W,** Held M, Lagergren J, Engstrand L, Blot WJ, McLaughlin JK, Nyren O. *Helicobacter pylori* infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. *J Natl Cancer Inst* 2004; **96**: 388-396
41 **Yuan JP**, Li T, Chen HB, Li ZH, Yang GZ, Hu BY, Shi XD, Tong SQ, Li YX, Guo XK. Analysis of gene expression profile in gastric cancer cells stimulated with *Helicobacter pylori* isogenic strains. *J Med Microbiol* 2004; **53**: 965-974
42 **Lu H,** Graham DY, Yamaoka Y. The *Helicobacter pylori* restriction endonuclease-replacing gene, hrgA, and clinical outcome: comparison of East Asia and Western countries. *Dig Dis Sci* 2004; **49**: 1551-1555
43 **Yamaoka Y**, Kudo T, Lu H, Casola A, Brasier AR, Graham DY. Role of interferon-stimulated responsive element-like element in interleukin-8 promoter in *Helicobacter pylori* infection. *Gastroenterology* 2004; **126**: 1030-1043
44 **Yamaoka Y,** Kwon DH, Graham DY. A M(r) 34,000 proinflammatory outer membrane protein (oipA) of *Helicobacter pylori*. *Proc Natl Acad Sci U S A* 2000; **97**: 7533-7538
45 **Varro A**, Noble PJ, Pritchard DM, Kennedy S, Hart CA, Dimaline R, Dockray GJ. *Helicobacter pylori* induces plasminogen activator inhibitor 2 in gastric epithelial cells through nuclear factor-kappaB and RhoA: implications for invasion and apoptosis. *Cancer Res* 2004; **64**: 1695-1702
46 **Nardone G**, Rocco A, Vaira D, Staibano S, Budillon A, Tatangelo F, Sciulli MG, Perna F, Salvatore G, Di Benedetto M, De Rosa G, Patrignani P. Expression of COX-2, mPGE-synthase1, MDR-1 (P-gp), and Bcl-xL: a molecular pathway of *H pylori*-related gastric carcinogenesis. *J Pathol* 2004; **202**: 305-312
47 **Zhang H**, Fang DC, Wang RQ, Yang SM, Liu HF, Luo YH. Effect of *Helicobacter pylori* infection on expression of Bcl-2 family members in gastric adenocarcinoma. *World J Gastroenterol* 2004; **10**: 227-230
48 **Ashktorab H**, Frank S, Khaled AR, Durum SK, Kifle B, Smoot DT. Bax translocation and mitochondrial fragmentation induced by *Helicobacter pylori*. *Gut* 2004; **53**: 805-813
49 **Rad R**, Dossumbekova A, Neu B, Lang R, Bauer S, Saur D, Gerhard M, Prinz C. Cytokine gene polymorphisms influence mucosal cytokine expression, gastric inflammation, and host specific colonisation during *Helicobacter pylori* infection. *Gut* 2004; **53**: 1082-1089
50 **Hartland S**, Newton JL, Griffin SM, Donaldson PT. A functional polymorphism in the interleukin-1 receptor-1 gene is associated with increased risk of *Helicobacter pylori* infection but not with gastric cancer. *Dig Dis Sci* 2004; **49**: 1545-1550
51 **Glas J**, Torok HP, Schneider A, Brunnler G, Kopp R, Albert ED, Stolte M, Folwaczny C. Allele 2 of the interleukin-1 receptor antagonist gene is associated with early gastric cancer. *J Clin Oncol* 2004; **22**: 4746-4752
52 **Chen A**, Li CN, Hsu PI, Lai KH, Tseng HH, Hsu PN, Lo GH,

Lo CC, Lin CK, Hwang IR, Yamaoka Y, Chen HC. Risks of interleukin-1 genetic polymorphisms and *Helicobacter pylori* infection in the development of gastric cancer. *Aliment Pharmacol Ther* 2004; **20**: 203-211

53 **Basak C,** Pathak SK, Bhattacharyya A, Mandal D, Pathak S, Kundu M. NF-kappaB- and C/EBPbeta-driven interleukin-1beta gene expression and PAK1-mediated caspase-1 activation play essential roles in interleukin-1beta release from *Helicobacter pylori* lipopolysaccharide-stimulated macrophages. *J Biol Chem* 2005; **280**: 4279-4288

54 **Osawa H**, Nakazato M, Date Y, Kita H, Ohnishi H, Ueno H, Shiiya T, Satoh K, Ishino Y, Sugano K. Impaired production of gastric ghrelin in chronic gastritis associated with *Helicobacter pylori*. *J Clin Endocrinol Metab* 2005; **90**: 10-16

55 **Konturek PC**, Brzozowski T, Pajdo R, Nikiforuk A, Kwiecien S, Harsch I, Drozdowicz D, Hahn EG, Konturek SJ. Ghrelin-a new gastroprotective factor in gastric mucosa. *J Physiol Pharmacol* 2004; **55**: 325-336

56 **Houghton J,** Stoicov C, Nomura S, Rogers AB, Carlson J, Li H, Cai X, Fox JG, Goldenring JR, Wang TC. Gastric cancer originating from bone marrow-derived cells. *Science* 2004; **306**: 1568-1571

S- Editor Wang J **L- Editor** Kumar M **E- Editor** Liu WF