World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i21.6386

World J Gastroenterol 2014 June 7; 20(21): 6386-6399
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

Helicobacter pylori infection: New pathogenetic and clinical aspects

Krisztina Hagymási, Zsolt Tulassay

Krisztina Hagymási, Zsolt Tulassay, 2nd Department of Internal Medicine, Semmelweis University, H-1088 Budapest, Hungary
Author contributions: Hagymási K and Tulassay Z drafted and wrote the manuscript; all authors read and approved the final manuscript.
Correspondence to: Krisztina Hagymási, MD, PhD, 2nd Department of Internal Medicine, Semmelweis University, H-1088 Budapest, Hungary. hagymasi.krisztina@med.semmelweis-univ.hu
Telephone: +36-1-2660926 Fax: +36-1-2664616
Received: September 28, 2013 Revised: January 5, 2014
Accepted: February 26, 2014
Published online: June 7, 2014

Abstract

Helicobacter pylori (*H. pylori*) infects more than half of the world's human population, but only 1% to 3% of infected people consequently develop gastric adenocarcinomas. The clinical outcome of the infection is determined by host genetic predisposition, bacterial virulence factors, and environmental factors. The association between *H. pylori* infection and chronic active gastritis, peptic ulcer disease, gastric cell carcinoma, and B cell mucosa-associated lymphoid tissue lymphoma has been well established. With the exception of unexplained iron deficiency anemia and idiopathic thrombocytopenic purpura, *H. pylori* infection has no proven role in extraintestinal diseases. On the other hand, there is data showing that *H. pylori* infection could be beneficial for some human diseases. The unpredictability of the long-term consequences of *H. pylori* infection and the economic challenge in eradicating it is why identification of high-risk individuals is crucial.

Key words: *Helicobacter pylori*; Virulence factor; Host factors; Gastroduodenal diseases; Extraintestinal disorders

Core tip: *Helicobacter pylori* (*H. pylori*) infects more than half of the world's human population. The association between *H. pylori* infection and chronic active gastritis, peptic ulcer disease, gastric cell carcinoma, and B cell mucosa-associated lymphoid tissue lymphoma, unexplained iron deficiency anemia and idiopathic thrombocytopenic purpura has been well established. *H. pylori* screening and treatment is a recommended gastric cancer risk reduction strategy in high-risk populations. The unpredictability of the long-term consequences of *H. pylori* infection and the economic challenge in eradicating it is why identification of high-risk individuals is crucial.

Hagymási K, Tulassay Z. *Helicobacter pylori* infection: New pathogenetic and clinical aspects. *World J Gastroenterol* 2014; 20(21): 6386-6399 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i21/6386.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i21.6386

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a micro-aerophilic, Gram-negative, slow-growing, spiral-shaped, and flagellated organism which infects more than half of the world's human population[1]. *H. pylori* colonization itself does not cause any symptoms, and fewer than 20% of all infected patients will develop symptoms from their infection[2]. Approximately 10% of infected individuals develop peptic ulcer disease, 1% to 3% develop gastric adenocarcinoma, and less 0.1% [mucosa-associated lymphoid tissue (MALT)] develop lymphoma[3].

The outcome of *H. pylori* infection may involve a combination of bacterial, host, and environmental factors. The association between *H. pylori* infection and chronic active gastritis, peptic ulcer disease, gastric cell carcinoma, and B cell MALT lymphoma has been well established. On the other hand *H. pylori* infection could

Table 1 Summary of the pathogenetic and preventive role of *Helicobacter pylori*

Pathogenetic role		Preventive role
Proven	**Suspected**	**Suspected**
Gastro-duodenal diseases	Gastro-intestinal diseases	Gastroesophageal diseases
Peptic ulcer	Pancreatic cancer	Gastroesophageal reflux disease
Gastric cancer	Colorectal adenoma/carcinoma	Esophageal adenocarcinoma
MALT lymphoma	Liver cirrhosis, hepatocellular carcinoma	
Extra-intestinal diseases	Extra-intestinal diseases	Extra-esophageal diseases
Immune thrombocytopenic purpura	Laryngeal cancer	Bronchial asthma
Iron deficiency anemia	Lung cancer	
	Metabolic syndrome/insulin resistance	
	Cardiovascular diseases/ischemic heart disease	
	Chronic urticaria	
	Henoch-Schönlein purpura	

MALT: Mucosa-associated lymphoid tissue.

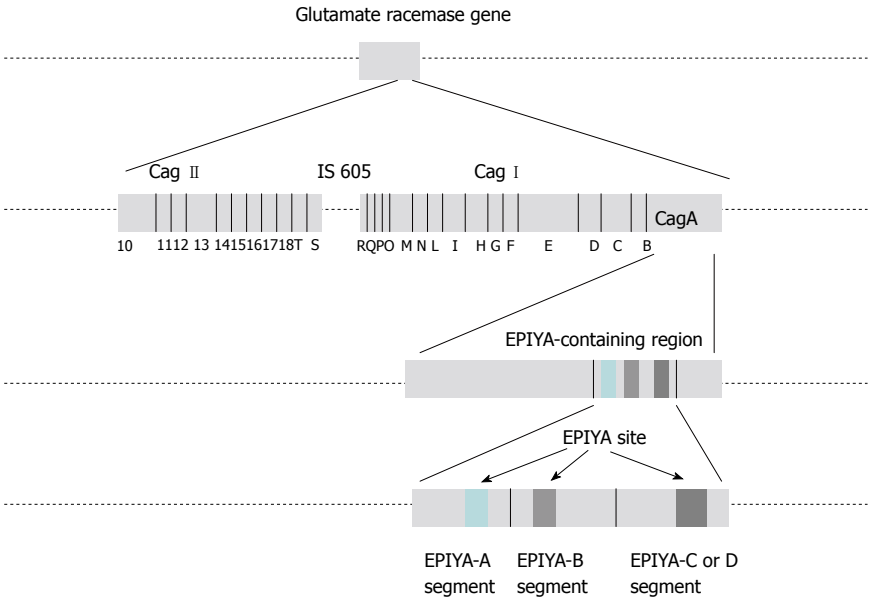

Figure 1 Cytotoxin-associated gene pathogenicity island. CagA: Cytotoxin-associated gene A product; EPIYA: Glutamate-proline-isoleucine-tyrosine-alanine.

be beneficial for humans[2] (Table 1).

PATHOGENETIC ASPECTS

Virulence factors of H. pylori

Bacterial virulence factors play a significant role in the outcome and progression of *H. pylori* infection[4]. The linkages of virulence factors may show how they interact with each other[5].

The cag pathogenicity island (cag PAI) contains 27-31 genes flanked by a 31-p direct repeats. *H. pylori* exhibits a high degree of genetic heterogeneity due to genomic rearrangements, gene insertions, and/or deletion[6].

At least 18 cag genes encode components of the bacterial type Ⅳ secretion system, which functions to export bacterial protein across the bacterial membrane and into host gastric epithelial cells. The presence of cag PAI (cag+) amplifies the risk for severe gastritis, atrophic gastritis, and distal gastric cancer in comparison with cag-deficient (cag-) bacteria[6].

CagA: Cytotoxin-associated gene A product (CagA) is translocated into the host cell by the type Ⅳ secretion system. Phosphorylation of CagA at the glutamate-proline-isoleucine-tyrosine-alanine (EPIYA) motifs by the host Abl and Src kinases results in morphological changes to the cell (the so-called "hummingbird phenotype"). Four EPIYA motifs (-A, -B, -C, and -D) are distinguished with different degrees of phosphorylation and geographical distribution[6]. EPIYA-A and EPIYA -B sites are less phosphorylated in comparison with EPIYA-C. EPIYA-C is typically found only in strains from Western countries (Europe, North America, and Australia), and is an indicator of gastric cancer risk. EPIYA-D is found in East Asian strains. EPIYA-D containing strains induce more relief of interleukin-8 (IL-8) from gastric epithelial cells[6] (Figure 1).

Phospho-CagA interacts with numerous intracellular effectors, including eukaryotic tyrosine phosphatase with sustained activation of extracellular signal-regulated kinases 1 and 2 (ERK ½), Crk adaptor, and C-terminal

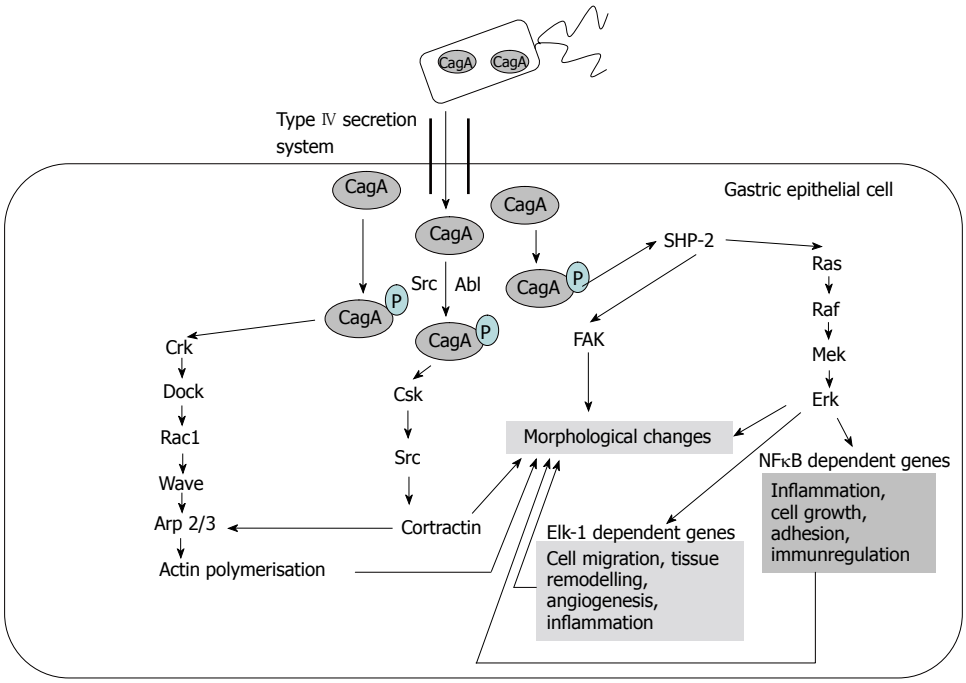

Figure 2 Targets of phosphorylated cytotoxin-associated gene A. Based on the article from Current Opinion in Microbiology, Hatakeyama M, SagA of CagA in *Helicobacter pylori* pathogenesis, 11, 30-37, Copyright (2008), with permission from Elsevier[7]. CagA: Cytotoxin-associated gene A product; NFκB: Nuclear factor κB; FAK: Focal adhesion kinase; Csk: C-terminal Src kinase.

Src kinase[6]. The activation of ERK and focal adhesion kinase with the tyrosine dephosphorylation of the actin binding proteins cortactin, ezrin, and vinculin leads to cell elongation[1,6] (Figure 2).

The targets of non-phosphorylated CagA comprise E-cadherin, β-catenin, hepatocyte growth factor receptor c-Met, phospholipase C gamma, adaptor protein Grb2, kinase partitioning-defective 1b/microtubule affinity-regulating kinase 2, epithelial tight junction scaffolding protein zonula occludens 1, and the transmembrane protein junctional adhesion molecule A. The main effects are pro-inflammatory and mitogenic cell-cell junction disruption and loss of cell polarity that may be important in gastric carcinoma development[1,6] (Figures 3 and 4).

Activity of CagA on tumor-suppressor pathways has also been investigated. CagA is able to modulate the *H. pylori* induced apoptotic signal, but the exact mechanism remains to be elucidated. The initial host response up-regulates p53 expression followed by the proteasomal degradation of p53[8].

Almost all *cagA*+ strains are classified as *vacA* s1 genotypes (either m1 or m2), whereas almost all *cagA*- strains are classified as the *vacA* s2/m2 strain (see below)[5]. Specific vacA genotypes of *H. pylori* strains are associated with a level of *in vitro* cytotoxin activity with clinical consequences[9].

Peptidoglycans: Peptidoglycans translocated by the cag secretion system interact with the nucleotide-binding oligomerization domain 1 (Nod1) molecule which leads to the activation of nuclear factor κB (NF-κB), pro-inflammatory secretion of interleukin-8 (IL-8), and β-defensin-2[6,10]. *H. pylori* enhances the phosphoinositide 3-kinase Akt signaling pathway, leading to decreased apoptosis and increased cell migration. NOD1 ligand binding can activate the interferon (IFN)-stimulated gene factor 3 signaling cascade, resulting in type I IFN production usually associated with protection against viral infection and possibly other mucosal infections[11].

VacA toxin: The cytotoxin gene *vacA* is present in all strains. The VacA cytotoxin induces the vacuolation, gastric epithelial barrier function disruption, disturbance of late endosomal compartments, and modulation of the inflammatory response. VacA reduces the mitochondrial transmembrane potential, releases cytochrome c from mitochondria, activates caspase 8 and 9, and induces apoptosis[6,12].

Binding of VacA to receptor-type protein tyrosine phosphatase (RPTPβ) regulates cell proliferation, differentiation, and adhesion, which all play a role in ulcerogenesis[13].

Variations in *vacA* gene structure (in the signal s: s1, s2, or in the middle regions m: m1, m2) make differences in vacuolating activity and specificity. The intermediate (i) region also plays role in the vacuolating activity of *H. pylori*. All s1, m1 strains were classified as i1 (vacuolating) type, and all s2, m2 strains were classified as i2 (non-vacuolating) type, while s1, m2 alleles could be i1 or i2. A novel intermediate variant (i3) has been identified. The fourth pathogenic region is d, a 69-81 bp-region between the m and i regions[1,5].

The variants in s and m regions seem to be a good indicator of clinical outcomes. However the roles of i

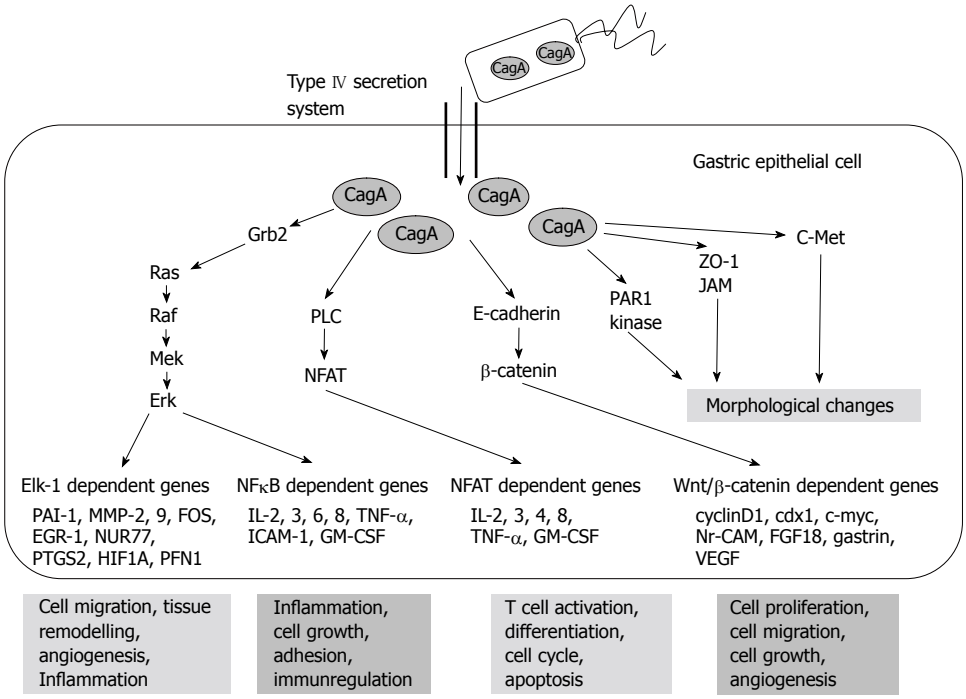

Figure 3 Targets of non-phosphorylated cytotoxin-associated gene a product. Based on the article from Current Opinion in Microbiology, Hatakeyama M, SagA of CagA in Helicobacter pylori pathogenesis, 11, 30-37, Copyright (2008), with permission from Elsevier[7]. CagA: Cytotoxin-associated gene A product; PLC: Phospholipase C gamma; PAR1: Kinase partitioning-defective 1b; ZO-1: Zonula occludens 1; JAM: Junctional adhesion molecule A; NFκB: Nuclear factor κB; TNF-α: Tumor necrosis factor-α; IL: Interleukin.

and d regions should be further investigated[5]. The s1, m1 strains can induce greater vacuolation, and are associated with peptic ulcer disease and gastric cancer in Western countries, but have no pathogenic role in East Asian countries[1,6]. vacA i1 strains were associated with gastric cancer in Iranian patients[14], but not in the East Asian or Southeast Asian populations[14]. i1 genotype appeared to be a better predictor of carcinoma-associated *H. pylori* strains than the s or m genotype[15]. In Western countries, d1 strains without the deletion of the d region are predictors of histological inflammation, atrophy, and an increased risk of peptic ulceration and gastric cancer, compared with the presence of the vacA s-, m-, and i-region strains[16].

Adhesins and outer membrane proteins: 4% of the *H. pylori* genome encodes for outer membrane proteins (BabA, BabB, SabA, and OipA) which function as adhesins and porins, and are implicated in complement resistance and immune regulation[17].

The blood group antigen binding adhesin BabA is thought to mediate host-bacterial interactions and maintain colonization of the *H. pylori* targeting human Lewis-b surface epitopes[18,19]. The *babA2* gene is associated with duodenal ulcer and gastric cancer. When in conjunction with cagA and vacA s1 alleles ("triple-positive strains"), it is associated with a greater risk of the more severe duodenal ulcer and gastric adenocarcinoma in Western populations[1,6,19].

Sialic acid-binding adhesin (SabA) binds to the carbohydrate structure sialyl-Lewis antigen expressed on the gastric epithelium. SabA can mediate the binding of *H. pylori* to neutrophils and erythrocytes, but the pathophysiological importance of these findings is uncertain[1]. SabA positive status was associated with increased gastric cancer risk and a negative status associated with duodenal ulceration[12].

The outer inflammatory protein (OipA) has a role in the increased expression of mucosal IL-1, -8, -17, tumor necrosis factor-α (TNF-α), and in gastric mucosal inflammation. Upregulation of matrix metalloproteinase 1, inhibition of glycogen synthase kinase 3β, and nuclear accumulation of β-catenin can influence carcinogenesis[6]. OipA positive status was significantly associated with duodenal ulcer and gastric cancer[12].

Others: Duodenal ulcer promoting gene (dupA) product induces the production of IL-8 and -12[5]. DupA may enhance duodenal ulceration and /or decrease gastric cancer development in some populations[1,5,6].
Variants of gene encoding flagellar proteins (flaA) of *H. pylori* may affect motility and colonization, and, therefore, the carcinogenic effect[6].

Annexin family members (AnxA1 and AnxA4) are involved in epithelial cell membrane repair response induced by *H. pylori*-generated VacA and CagA-independent plasma membrane disruption. Plasma membrane disruption and AnxA4 can promote cell proliferation[19].

TNF-α-inducing protein (Tipα) binds to cell-surface nucleolin and then enters the gastric cancer cells where

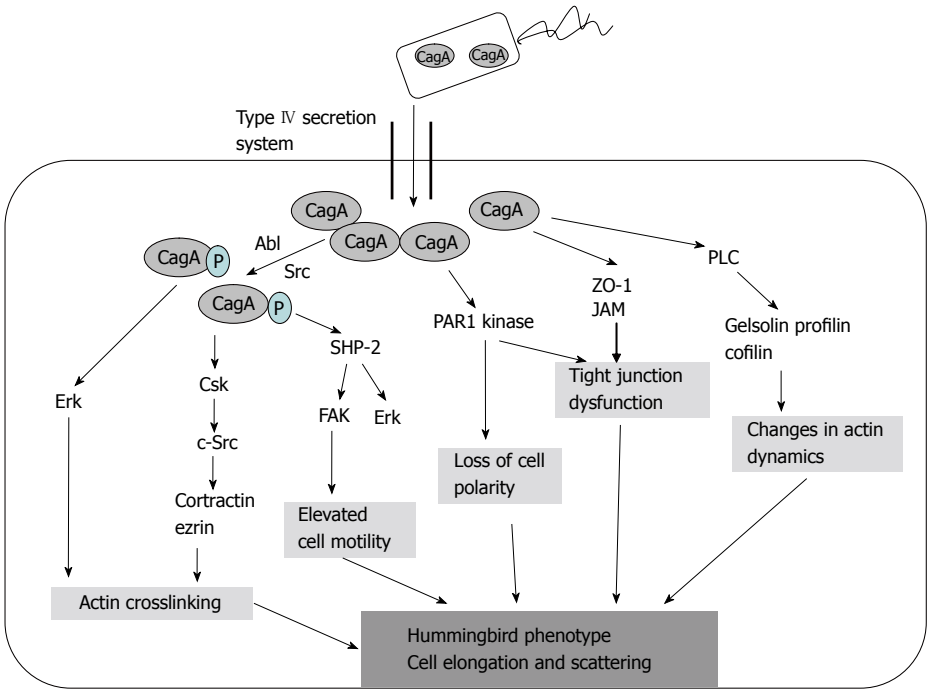

Figure 4 Development of "hummingbird phenotype". CagA: Cytotoxin-associated gene A product; PLC: Phospholipase C gamma; PAR1: Kinase partitioning-defective 1b; ZO-1: Zonula occludens 1.

TNF-α and chemokine gene expressions are induced by NF-κB activation in a cag PAI independent manner[20].

Bacterial factors like urease, AmiE, AmiF, hydrogenase, and arginase are essential for *H. pylori* survival in the acidic gastric environment[4].

Immune response to *H. pylori*: The host's innate and adaptive immune system plays a crucial role in the initiation and progression of *H. pylori* infection[21].

Innate immunity effectors and a complex mixture of T helper (Th) 1, Th17, and regulatory T cells (Treg) adaptive immunity effectors are involved in *H. pylori* infection[22].

H. pylori initially targets gastric epithelial cells which form part of the innate immune response via signaling through pattern recognition receptors, such as Toll-like receptors (mainly TLR2)[21].

The neutrophil-activating protein of *H. pylori* polarizes Th1 cells, stimulating IL-12 and IL-23 secretion from neutrophils and macrophages. Th1 cytokines, such as gamma interferon (IFN-γ) and TNF-α, can increase the release of pro-inflammatory cytokines and augment apoptosis induced by *H. pylori*[22,23].

IL-17 expressing Th17 cells are important in the pro-inflammatory immune response to *H. pylori*. Th17 cells produce Il-17, IL-21, and IL-22 cytokines[6]. *H. pylori* infected macrophages produce IL-6, IL-23, and transforming growth factor (TGF)-β, which are required for Th17 cell development and maintenance[6,21]. The literature on Th1 and Th17 *H. pylori*-associated gastric pathology is confusing and requires intensive investigation[6].

Tregs (formerly suppressor T cells) are also implicated in the pathogenesis of *H. pylori* infection. TGF-β and IL-18 are responsible for Treg development[21]. *H. pylori*-specific Tregs suppress memory T cell responses that prolong the infection[6]. Tregs suppress the inflammatory reaction driven by IL-17, thereby also favoring bacterial persistence[24].

Antimicrobial defense of macrophages is nitric oxide (NO) dependent. *H. pylori*'s arginase enzyme can compete with macrophages for the inducible nitric oxide synthase (iNOS) substrate L-arginine so that host NO production is impaired; this leads to enhanced bacterial survival. *H. pylori* can evade macrophage phagocytosis. VacA protein prevents the fusion of phagosomes with lysosomes needed for phagocytosis. Fused phagosomes contain large numbers of live bacteria[6].

The role of B cells in the host response to *H. pylori* has been suggested[21]. Immunoglobulin (Ig) G and IgA antibody release from B cells in response to *H. pylori* may be involved in protective immunity, however it was suggested this antibody-mediated response may be counterproductive. B cells can also produce autoreactive antibodies that may be pathogenic[6]. B cell activation and survival may have implications for MALT lymphoma development[6].

CLINICAL ASPECTS

Gastroduodenal diseases

Peptic ulcer: Some *H. pylori* colonized individuals may develop corpus gastritis associated with gastric hypochlorhydria, gastric atrophy, gastric ulcer, and an increased risk of gastric cancer. Conversely, others may develop antral-predominant gastritis, which is associated with gastric hyperchlorhydria and an increased risk of duodenal ulcer[8,25].

Since the discovery of *H. pylori* in the 1980s, the availability of effective eradication therapy has led to a decline in recurrent peptic ulcer disease and its complications. The pathogenetic role of *H. pylori* in 90% of duodenal ulcers and 80% of gastric ulcers is proven[26,27]. Effective eradication decreased the yearly recurrence rate of duodenal and gastric ulcers from 80% and 60%, respectively, to less than 5%[28].

Gastric cancer: *H. pylori* is a class I carcinogen in humans[1]. It is considered to be the most common aetiological factor of infection-related cancers (followed by human papilloma, hepatitis B and C, Epstein-Barr, human immunodeficiency, and human herpesvirus-8)[1,29]. *H. pylori* infection-related cancer represents 5.5% of the global cancer burden[6].

Gastric cancer develops in 2.9% of *H. pylori* infected patients[30]. *H. pylori* infection is responsible for about 75% of all non-cardia gastric cancers and 63.4% of all stomach cancers worldwide[1]. *H. pylori* infection also plays a fundamental role in non-cardia gastric carcinogenesis, but its association with cardia cancer is still uncertain[31].

The prevalence of infection is statistically significantly much higher in patients with intestinal-type gastric cancer (89.2%) compared to the diffuse-type (31.8%)[32]. *H. pylori* infection is regarded as the trigger of intestinal-type gastric adenocarcinoma[33]. According to Correa and Piazuelo, intestinal-type gastric carcinogenesis progresses as follows: normal gastric mucosa - no atrophic gastritis - multifocal atrophic gastritis without intestinal metaplasia - intestinal metaplasia of complete (small intestine) type - low-grade dysplasia - high-grade dysplasia - invasive adenocarcinoma[34]. Altered cell proliferation, apoptosis, epigenetic modifications to the tumor suppressor genes, oncogene activation, and dysregulation of DNA repair may occur and eventually lead to inflammation-associated carcinogenesis[35].

Eradication of *H. pylori* infection decreases the risk of premalignant lesions and gastric cancer in infected individuals[36-38]. Follow-up endoscopy and histology is crucial, even in patients with apparently non-malignant gastric ulcers, in improving the malignancy detection rate in populations with a high prevalence of gastric cancer[39].

H. pylori plays a role in the development and progression of gastric (MALT) lymphoma[40]. The average prevalence of *H. pylori* infection in MALT lymphoma was 79%; it was higher in low-grade (79%) than in high-grade (60%) cases[41]. Treatment for localized stage I gastric MALT lymphoma with *H. pylori* infection is eradication[40]. Eradication of *H. pylori resulted in* a complete remission in 60%-80% of patients with MALT lymphoma[42,43], and a 10-year sustained remission in up to 64% of cases[44].

The carcinogenic effect of *H. pylori* can be modified by dietary and environmental factors. *H. pylori* infection is more frequent in less developed Asian countries (*e.g.*, India, Bangladesh, Pakistan, and Thailand) in comparison with the more developed Asian countries (*e.g.*, Japan and China). However, the frequency of gastric cancer is paradoxically very low in these less developed regions than in Japan and China (the so-called "Asian enigma")[33,45]. Several other large populations with high infection prevalence show a very low rate of gastric cancer. The so-called "African enigma" remains unexplained as well, but it does verify that not all *H. pylori* infected patients have an increased risk of gastric cancer[32,33,46].

Host and environmental factors also affect the development of gastroduodenal diseases in *H. pylori* infected individuals[6,47]. Individuals with a high-expression of IL-1β polymorphisms (C-T or T-C transitions, at positions -511, -31, and +3954 base pairs from the transcriptional start site) have an increased risk for hypochlorhydria, gastric atrophy, and distal gastric adenocarcinoma in comparison with low-expression polymorphisms; they have no effect on cancers associated with high acid exposure such as esophageal adenocarcinomas and some cardia cancers[47,48]. The combined effects of pro-inflammatory IL-1 genotypes and *H. pylori* bacterial virulence factors have been reported[48].

Gene polymorphisms (-308 G > A) of the pro-inflammatory cytokine TNF-α that increase the expression of the cytokine and polymorphisms (promoter polymorphisms at positions -592, -819, and -1082) that reduce the production of the anti-inflammatory cytokine (IL-10) have been associated with an increased risk of distal gastric cancer[48-50].

The effects of pro-inflammatory genotypes (IL-1β, TNF-α and IL-10) are additive[6,50].

High dietary salt intake increases the risk of gastric cancer by directly damaging gastric mucus and mucosa, improving temporary epithelial proliferation, increasing the incidence of endogenous mutations, upregulating cytokine production, and *H. pylori* gene expression modulation, especially that of virulence factors[51-53].

Co-infection with helminths (*Ascaris lumbricoides*) and *Toxoplasma gondii* reduces the severity of *H. pylori*-induced gastritis via a reduced Th1 response with higher levels of Th2 cytokines[54].

Fruit and vegetables are rich sources of carotenoids, vitamin C, folate, and phytochemicals, which may modulate xenobiotic-metabolizing enzymes and have antioxidant activity, thereby playing a preventive role in carcinogenesis[6,55-57].

Smoking is an established risk factor for gastric cancer. Swallowed carcinogenic substances (nitrosamine and other nitroso compounds), greater concentrations of smoking-related DNA adducts in the gastric mucosa, lower levels of free radical scavengers (ascorbic acid and β-carotene), and increased mRNA expression of chemokines in the gastric mucosa are in the background[58].

Pancreatic cancer

Epidemiological studies have suggested that *H. pylori* might be involved in the pathogenesis of pancreatic cancer (OR = 1.87, 2.1), however results are inconsistent[59,60]. A meta-analysis showed significant association between *H. pylori* seropositivity and development of pancreatic

Table 2 Putative pathomechanisms of *Helicobacter pylori*

Disease	Putative pathomechanisms
Pathogenetic role	
Pancreatic cancer	Inflammatory cytokine ↑[61]
	Angiogenic factors ↑[61]
	Reactive oxygen species ↑[61]
	Somatostatin synthesis ↓[64,65]
	Secretin release ↑[64,65]
	Basal pancreatic bicarbonate output ↑[64,65]
	Bacterial overgrowth, production of N-nitroso compounds ↑[66]
	Absorption of antioxidants ↓[67]
Colorectal adenoma/carcinoma	Direct damage[69]
	Inflammation ↑[69]
	Bacterial overgrowth, bacterial fermentation (ammonia)↑[69-71,74,75]
	NO release ↑[76]
	Hypergastrinemia[68,69]
Hepatobiliary disease	Ammonia ↑[90]
	Endotoxemia[90]
	Inflammation ↑[90]
	Hepatic fibrosis ↑[87]
	Hepatoma cell adhesion and invasion ↑[91]
Laryngeal cancer	Sensitivity to smoke and dust ↑[92]
	Cell proliferation ↑[92]
	Apoptosis ↓[92]
Lung cancer	Direct damage[97]
	Sensitivity to smoke and dust ↑[98]
	Inhalation of gastrin and urea[95]
	Hypergastrinemia[94]
	Activation of docking protein p130cas[95]
	Inflammation ↑[94]
Insulin resistance/metabolic syndrome	Inflammation ↑[103,105]
	Vasoconstrictor factors ↑[103,105]
	Adiponectin ↓[104]
Atherogenesis	Inflammation ↑[108]
	Autoimmunity[108]
	Fibrinogen ↑[112]
	Platelet aggregation ↑[114]
Chronic urticaria	Vascular permeability ↑[83]
	Complement consumption ↑[83]
	Pathogenetic antibodies ↑[83]
Henoch-Schönlein purpura	IgA ↑[82]
	Cryoglobulins ↑[82]
	C3 ↓[82]
Possible preventive role	
Gastroesophageal reflux disease	Sympathetic tone ↑[128]
	Cholinergic stimulation[128]
Esophageal adenocarcinoma	Sympathetic tone ↑[128]
	Cholinergic stimulation[128]
	Acid production ↓[129]
Bronchial asthma	Polarization of Th-1 ↓[131]
	Allergic Th-2 response ↓[131]
	Tregs ↓[132,133]
	Interleukin-1 receptor associated kinase M (IRAK-M) ↑[133]

↑: Increase; ↓: Decrease.

cancer (pooled adjusted OR = 1.38), but further research is needed to confirm this result[61,62].

Despite good scientific reasoning for the involvement of *H. pylori* in pancreatic diseases, direct pancreatic infection seems unlikely[63] (Table 2).

Colorectal adenoma/carcinoma

On the basis of the epidemiological results showing high mortality rates from gastric and colorectal cancer in similar areas, it can be speculated that gastric cancer and colorectal cancer have common risk factors like *H. pylori* infection[68]. Although the role of *H. pylori* in colorectal carcinogenesis has been widely examined, the association has remained inconclusive[69]. Several studies demonstrated conflicting positive and negative associations[68,69]. A meta-analysis showed that *H. pylori* infection was associated with an increased risk of colorectal adenoma (OR = 1.66) and colorectal cancer (OR = 1.39), however there was significant heterogeneity among the studies[70]. The inconsistent results might be due to sample bias, small sample size, varying frequencies of cagA+ strains in the study population, incomplete colonoscopies, and evaluation of *H. pylori* infection with the IgG serum test[69].

H. pylori was detected in colorectal carcinoma tissue in a pilot study[71]. Higher prevalence was proven in adenoma and colorectal cancer compared with control[72,73]. *H. pylori* was more prevalent in moderate/severe dysplastic adenomas compared with mild dysplasia, and in tubular and tubulovillous adenoma compared with villous type[72].

The pathogenetic mechanisms of *H. pylori* induced colorectal carcinogenesis are not fully understood[69] (Table 2). However, not every study confirms the correlation between atrophic gastritis, hypergastrinemia, and colorectal cancer[68]. Conversely, atrophic gastritis and hypergastrinemia demonstrated a significant elevation in the odds ratio (3.15) for rectal cancer[68]. Overall, chronic atrophic gastritis did not seem to contribute to an increase in colorectal adenoma risk. Chronic atrophic gastritis and its progression appear to further increase the risk for proximal colorectal adenoma formation[77]. The inconsistent results correlating hypergastrinemia and colorectal carcinogenesis may be explained by the fact that gastrin precursors (progastrin and glycine-extended gastrin) act as important promoters of colorectal carcinogenesis, but cannot be measured by most commercially available assays[77,78].

Concomitant *H. pylori* infection with metabolic syndrome further increases the possibility of colorectal adenoma formation; however the pathomechanism for this possible association is still unclear[69]. Insulin might exert proliferative effects on colonic tumor cells directly or indirectly via the insulin-like growth factor pathway[79]. Chronic inflammation, increased pro-inflammatory cytokine production, and decreased anti-inflammatory adiponectin production might be associated with carcinogenesis[69,80]. Triglycerides are energy sources for cancer cell growth and are linked with increased synthesis of bile acids, which have a carcinogenesis promoting effect[81].

Extra-intestinal diseases

It has been shown that *H. pylori* may play a potential pathogenic role in extra-intestinal diseases via multiple mechanisms[82]. Atrophic gastritis caused by infection, an increase in gastric vascular permeability and therefore increased exposure to alimentary antigens, release of inflammatory mediators, and systemic immune responses (auto-immunity, pro-inflammatory substances, and im-

mune complex formation induced by molecular mimicry and cross-reactive antibodies) have been suspected in the background[82,83].

With the exception of unexplained iron deficiency anemia (evidence level 1a) and idiopathic thrombocytopenic purpura (evidence level 1b), *H. pylori* infection has no proven role in other extra-intestinal diseases[82,84,85].

Hepatobiliary diseases

Helicobacter DNA has been detected in hepatic tissues from patients with various hepatobiliary diseases, hepatitis C virus-related chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC)[86,87]. The association between *H. pylori* and Child-Pugh classification is inconsistent[87]. It can be proposed that *H. pylori* infection may play a role in hepatic carcinogenesis as well[88]. The odds ratio for the association between *H. pylori* infection and the risk of HCC was 13.63[89] (Table 2).

Respiratory tract disorders

Laryngeal cancer: Colonization of bacteria in the upper aerodigestive tract was confirmed, however the relationship between *H. pylori* infection and laryngeal cancer risk have produced conflicting results. Meta-analysis showed a 2.03-fold increased risk[92].

H. pylori was detected in larynx cancerous tissue. The presence of the cagA gene in larynx cancer tissues significantly decreased survival rate and increased the possibility of disease recurrence[93] (Table 2).

Lung cancer: The results of previous studies of *H. pylori* seropositivity and lung cancer are inconclusive[94], with an odds ratio between 1.24 and 17.78 on the basis of the epidemiological studies[95]. The NHANES study observed an inverse association between *H. pylori* and lung cancer in older participants, with a significant inverse association for cagA+ strains; this was without histological examination[96]. A case-control study found no evidence of an association between *H. pylori* and lung cancer in Finish male smokers. Neither overall *H. pylori* seropositivity nor CagA-specific *H. pylori* seropositivity were associated with lung cancer[94]. Causal relationships must be confirmed with exact determination of smoking status[95] (Table 2).

Insulin resistance and metabolic syndrome

Epidemiological studies showed significant associations with metabolic syndrome (OR = 1.39)[99,100]. Furthermore, multiple linear regression analysis showed that *H. pylori* seropositivity was significantly associated with higher systolic blood pressure, lower high-density lipoprotein (HDL)-cholesterol level, and higher low-density lipoprotein (LDL)-cholesterol level[99]. It has been suggested that *H. pylori* eradication could lead to an improvement of atherogenic blood lipid profile, insulin resistance, and low-grade inflammation, which were deduced from a decreased C-reactive protein level[101]. Other studies did not find an association between *H. pylori* infection and insulin resistance[102,103].

The relationship between *H. pylori* infection and metabolic syndrome is both poorly understood[104] (Table 2) and controversial[106-108].

Cardiovascular diseases

Studies investigating the pathogenetic role of *H. pylori* in cardiovascular diseases have produced conflicting results[108-111]. A meta-analysis of 18 epidemiological studies involving 10,000 patients did not find any positive association between *H. pylori* and cardiovascular risk factors and coronary heart diseases[112]. A higher prevalence of more virulent cagA+ *H. pylori* was reported in patients with ischemic heart disease, unstable angina, acute myocardial infarction, and restenosis after percutaneous transluminal coronary angioplasty and essential hypertension[108,111,113].

Evidence on the relationship between *H. pylori* infection and ischemic heart disease is weak, with some inconclusive, albeit plausible, mechanisms (Table 2). There are also no adequate interventional studies done to demonstrate that *H. pylori* eradication is associated with a lower incidence of ischemic heart disease[108].

Dermatological disorders

Chronic urticaria: A correlation between *H. pylori* infection and chronic urticaria has been suggested (Table 2). *H. pylori* eradication in patients with chronic urticaria leads to symptomatic improvement in some patients, while others showed no improvement[83].

Hematological disorders

Immune thrombocytopenic purpura: The prevalence of *H. pylori* infection in patients with immune thrombocytopenic purpura (ITP) is significantly higher than that in age- and gender-matched controls[108,115,116]. The most plausible mechanism is cross-mimicry involving *H. pylori,* platelet antigens, and infected host factors (antibody production cross-reacts with platelet glycoprotein antigens)[108,117].

Eradication of *H. pylori* results in an increasing platelet count in nearly half of infected ITP patients, although geographical differences in the efficacy of eradication were also presumed[83,115,116]. The European Helicobacter Study Group consensus in 2012 and the Second Asia-Pacific Consensus Guidelines have recommended *H. pylori* infection eradication in patients with chronic idiopathic thrombocytopenic purpura[84,85]. However, larger randomized controlled trials with long-term follow-up are still required before a firm conclusion can be drawn[108].

Henoch-Schönlein purpura: A study in China found increasing evidence suggesting that Henoch-Schönlein purpura (HSP), especially abdominal HSP, might be associated with *H. pylori* infection (OR = 4.62); this underlines the necessity of screening *H. pylori* infection in children with HSP with gastrointestinal manifestations[82].

It was found that eradication of *H. pylori* infection resulted in prompt resolution of the HSP, or at least prevented its recurrence[118].

More investigations are needed to confirm the pathogenetic role of *H. pylori* in HSP (Table 2). HSP children with serious gastrointestinal symptoms must be screened and treated for *H. pylori* infection[82].

Iron deficiency anemia: Several epidemiological studies have shown lower ferritin levels among patients with *H. pylori* infection, although there were studies that produced a negative association[108]. Meta-analyses showed an association between *H. pylori* infection and iron deficiency anemia (IDA)[119,120]. *H. pylori* eradication improves iron absorption[121].

Possible pathomechanisms are: increased iron loss due to active hemorrhage secondary to gastritis, peptic ulcer, gastric cancer, reduced iron absorption caused by achlorhydria induced by chronic pangastritis, reduced secretion of ascorbic acid to the gastric mucosa, and iron utilization for protein synthesis by the bacterium for colonization in the host environment[122]. Elevated serum prohepcidin might also indicate the role of inflammation in its aetiology[123].

Testing and eradication of *H. pylori* for unexplained IDA are supported by the current evidence and approved by the Maastricht Ⅳ Consensus and the Second Asia-Pacific Consensus Guidelines[84,85]. However, larger sample randomized controlled trials are necessary to clarify the reason why only a small proportion of *H. pylori*-positive patients develop IDA[108].

Possible beneficial clinical consequences of H. pylori infection

Gastroesophageal reflux disease/esophageal adenocarcinoma: A meta-analysis showed that *H. pylori* infection displays a negative association with the development of endoscopic gastroesophageal reflux disease (GORD). Eradication of the infection may be a risk factor for development of *de novo* GORD[124].

H. pylori infection protects against gastroesophageal reflux[2]. *H. pylori*-induced corpus gastritis and profound suppression of gastric acid secretion have also been shown to prevent patients from developing GORD[125]. cagA+ *H. pylori* strains have a more protective effect against GORD[126], and it was found that *H. pylori* infection was inversely associated with Barrett's esophagus[127].

The Maastricht consensus Ⅳ confirmed a negative association between the prevalence of *H. pylori* and the severity of GORD. The consensus stated that *H. pylori* status exerts no effect on symptom severity, recurrence, or treatment efficacy in GORD. *H. pylori* eradication does not exacerbate pre-existing GORD or affect treatment efficacy[85].

Esophageal adenocarcinoma risk due to *H. pylori* infection was 0.58-fold, and squamous cell carcinoma risk was 0.80-fold compared with that of controls. Compared with cagA- *H. pylori*, cagA+ *H. pylori* markedly decreased esophageal cancer risk[129].

The underlying mechanism in the background of the protective effect of *H. pylori* against GORD is not fully understood (Table 2).

H. pylori infection acts as neither a preventive factor nor a risk factor for squamous cell carcinoma. This discrepancy might be due to the relatively small number and heterogeneity of the included studies[129].

There is further need to assess the benefits of *H. pylori* in connection with GORD and its complications.

Bronchial asthma: An infection in the early phase of life is essential for the normal maturation of the immune system, achieving a balance between T-helper type 1 (protective immunity) and T-helper type 2 (allergic diseases) cytokine responses, which can reduce the risk of atopy later[129].

H. pylori infection might play a role in the development of chronic bronchitis, bronchiectasis, tuberculosis, and lung cancer[130]. Moreover, *H. pylori* might have an influence on the developing immune system, which might reduce the risk of asthma in later life[131].

The associations between *H. pylori* and asthma were contradictory. Inverse associations were reported, but other studies demonstrated different results[131]. A meta-analysis found weak evidence (OR = 0.81, 0.84) for an inverse association between *H. pylori* infection and asthma in children and adults, respectively[131,132]. Another meta-analysis failed to prove a significant association between *H. pylori* infection and asthma risk[130].

The mechanism of the preventive effect of *H. pylori* on asthma has been unambiguous (Table 2).

It seemed that *H. pylori* infection (especially cagA+ strains) may prevent children from developing asthma, but must be studied in the future[131] due to the inconsistent result[134].

CONCLUSION

The clinical outcome of *H. pylori* infection is determined by host genetic predisposition, bacterial strain factors, and environmental factors[1]. Bacterial virulence factors (VacA, CagA) can modulate the immune response involved in the initiation of the carcinogenesis in the stomach. Host genetic factors including IL-1β, IL-10, and TNF-α influence the inflammatory response and the exasperation of mucosal damage. Environmental factors, including salt intake and smoking tobacco, are well-known harmful aetiological factors. The ingestion of fruit and vegetables has some protective effect[135].

The mechanisms of *H. pylori*-associated gastric carcinogenesis are still poorly defined; further recognition may provide possibilities to develop effective strategies for gastric cancer prevention and treatment[1].

Indications for *H. pylori* therapy have been extended and now include idiopathic thrombocytopenic purpura, iron deficiency anemia, and vitamin B12 deficiency. New data are presented on the role of *H. pylori* in neurodegenerative disorders and in metabolic syndrome. *H. pylori* is associated with a small increase in the risk for colorectal adenoma and colon cancer[80] (Table 3).

Table 3 Other possible pathogenetic roles of *Helicobacter pylori*[83,94,110,117,136,137]

Renal diseases
Renal resistive index, proteinuria
Hepatobiliary diseases
Alcoholic damages of the liver, cholestatic autoimmune liver diseases (primary biliary diseases, primary sclerosing cholangitis), cholelithiasis, cholangiocellular carcinoma
Pancreatic disorders
Autoimmune pancreatitis
Intestinal diseases
Enteric diseases, inflammatory bowel diseases
Neurological diseases
Alzheimer-disease, idiopathic parkinsonism
Dermatological diseases
Alopecia areata, atopic dermatitis, lichen planus, chronic prurigo multiformis, nodular prurigo, pruritus, psoriasis, recurrent aphthous stomatitis, rosacea, Sweet's syndrome
Ophthalmological diseases
Glaucoma, central serous chorioretinopathy, uveitis, blepharitis
Autoimmune disorders
Autoimmune thyroiditis, Behçet's disease, Sjögren's syndrome, progressive systemic sclerosis
Others
Impaired bioavailability of medication such as thyroxin and l-dopa, pre-eclampsia, chronic prostatitis, growth retardation

H. pylori screening and treatment is a recommended gastric cancer risk reduction strategy in high-risk populations. In low-risk populations for gastric cancer, *H. pylori* screening is not recommended[84]. The removal of *H. pylori* from a large section of the population may be economically difficult, and the long-term consequences are still unpredictable. Identification of high-risk individuals is thus very important[40].

REFERENCES

1 **Wen S**, Moss SF. Helicobacter pylori virulence factors in gastric carcinogenesis. *Cancer Lett* 2009; **282**: 1-8 [PMID: 19111390 DOI: 10.1016/j.canlet.2008.11.016]
2 **Mishra S**. Is Helicobacter pylori good or bad? *Eur J Clin Microbiol Infect Dis* 2013; **32**: 301-304 [PMID: 23132690 DOI: 10.1007/s10096-012-1773-9]
3 **Peek RM**, Crabtree JE. Helicobacter infection and gastric neoplasia. *J Pathol* 2006; **208**: 233-248 [PMID: 16362989 DOI: 10.1002/path.1868]
4 **Molnar B**, Galamb O, Sipos F, Leiszter K, Tulassay Z. Molecular pathogenesis of Helicobacter pylori infection: the role of bacterial virulence factors. *Dig Dis* 2010; **28**: 604-608 [PMID: 21088410 DOI: 10.1159/000320060]
5 **Yamaoka Y**. Pathogenesis of Helicobacter pylori-Related Gastroduodenal Diseases from Molecular Epidemiological Studies. *Gastroenterol Res Pract* 2012; **2012**: 371503 [PMID: 22829807 DOI: 10.1155/2012/371503]
6 **Wroblewski LE**, Peek RM, Wilson KT. Helicobacter pylori and gastric cancer: factors that modulate disease risk. *Clin Microbiol Rev* 2010; **23**: 713-739 [PMID: 20930071 DOI: 10.1128/CMR.00011-10]
7 **Hatakeyama M**. SagA of CagA in Helicobacter pylori pathogenesis. *Curr Opin Microbiol* 2008; **11**: 30-37 [PMID: 18243773 DOI: 10.1016/j.mib.2007.12.003]
8 **Ruggiero P**. Helicobacter pylori infection: what's new. *Curr Opin Infect Dis* 2012; **25**: 337-344 [PMID: 22555448 DOI: 10.1097/QCO.0b013e3283531f7c]
9 **Atherton JC**, Cao P, Peek RM, Tummuru MK, Blaser MJ, Cover TL. Mosaicism in vacuolating cytotoxin alleles of Helicobacter pylori. Association of specific vacA types with cytotoxin production and peptic ulceration. *J Biol Chem* 1995; **270**: 17771-17777 [PMID: 7629077 DOI: 10.1074/jbc.270.30.17771]
10 **Backert S**, Naumann M. What a disorder: proinflammatory signaling pathways induced by Helicobacter pylori. *Trends Microbiol* 2010; **18**: 479-486 [PMID: 20863705 DOI: 10.1016/j.tim.2010.08.003]
11 **Watanabe T**, Asano N, Fichtner-Feigl S, Gorelick PL, Tsuji Y, Matsumoto Y, Chiba T, Fuss IJ, Kitani A, Strober W. NOD1 contributes to mouse host defense against Helicobacter pylori via induction of type I IFN and activation of the ISGF3 signaling pathway. *J Clin Invest* 2010; **120**: 1645-1662 [PMID: 20389019 DOI: 10.1172/JCI39481]
12 **Yamaoka Y**, Ojo O, Fujimoto S, Odenbreit S, Haas R, Gutierrez O, El-Zimaity HM, Reddy R, Arnqvist A, Graham DY. Helicobacter pylori outer membrane proteins and gastroduodenal disease. *Gut* 2006; **55**: 775-781 [PMID: 16322107 DOI: 10.1136/gut.2005.083014]
13 **Fujikawa A**, Shirasaka D, Yamamoto S, Ota H, Yahiro K, Fukada M, Shintani T, Wada A, Aoyama N, Hirayama T, Fukamachi H, Noda M. Mice deficient in protein tyrosine phosphatase receptor type Z are resistant to gastric ulcer induction by VacA of Helicobacter pylori. *Nat Genet* 2003; **33**: 375-381 [PMID: 12598897 DOI: 10.1038/ng1112]
14 **Rhead JL**, Letley DP, Mohammadi M, Hussein N, Mohagheghi MA, Eshagh Hosseini M, Atherton JC. A new Helicobacter pylori vacuolating cytotoxin determinant, the intermediate region, is associated with gastric cancer. *Gastroenterology* 2007; **133**: 926-936 [PMID: 17854597 DOI: 10.1053/j.gastro.2007.06.056]
15 **Ogiwara H**, Graham DY, Yamaoka Y. vacA i-region subtyping. *Gastroenterology* 2008; **134**: 1267; author reply 1268 [PMID: 18395110 DOI: 10.1053/j.gastro.2007.11.062]
16 **Ogiwara H**, Sugimoto M, Ohno T, Vilaichone RK, Mahachai V, Graham DY, Yamaoka Y. Role of deletion located between the intermediate and middle regions of the Helicobacter pylori vacA gene in cases of gastroduodenal diseases. *J Clin Microbiol* 2009; **47**: 3493-3500 [PMID: 19726606 DOI: 10.1128/JCM.00887-09]
17 **Dossumbekova A**, Prinz C, Gerhard M, Brenner L, Backert S, Kusters JG, Schmid RM, Rad R. Helicobacter pylori outer membrane proteins and gastric inflammation. *Gut* 2006; **55**: 1360-1361; author reply 1361 [PMID: 16905702]
18 **Gerhard M**, Lehn N, Neumayer N, Borén T, Rad R, Schepp W, Miehlke S, Classen M, Prinz C. Clinical relevance of the Helicobacter pylori gene for blood-group antigen-binding adhesin. *Proc Natl Acad Sci USA* 1999; **96**: 12778-12783 [PMID: 10535999 DOI: 10.1073/pnas.96.22.12778]
19 **Lin LL**, Huang HC, Ogihara S, Wang JT, Wu MC, McNeil PL, Chen CN, Juan HF. Helicobacter pylori Disrupts Host Cell Membranes, Initiating a Repair Response and Cell Proliferation. *Int J Mol Sci* 2012; **13**: 10176-10192 [PMID: 22949854 DOI: 10.3390/ijms130810176]
20 **Suganuma M**, Watanabe T, Yamaguchi K, Takahashi A, Fujiki H. Human gastric cancer development with TNF-α-inducing protein secreted from Helicobacter pylori. *Cancer Lett* 2012; **322**: 133-138 [PMID: 22459353 DOI: 10.1016/j.canlet.2012.03.027]
21 **Ihan A**, Pinchuk IV, Beswick EJ. Inflammation, immunity, and vaccines for Helicobacter pylori infection. *Helicobacter* 2012; **17** Suppl 1: 16-21 [PMID: 22958150 DOI: 10.1111/j.1523-5378.2012.00977.x]
22 **Müller A**, Solnick JV. Inflammation, immunity, and vaccine development for Helicobacter pylori. *Helicobacter* 2011; **16** Suppl 1: 26-32 [PMID: 21896082 DOI: 10.1111/j.1523-5378.2011.00877.x]
23 **Tsai HF**, Hsu PN. Interplay between Helicobacter pylori and immune cells in immune pathogenesis of gastric inflam-

mation and mucosal pathology. *Cell Mol Immunol* 2010; **7**: 255-259 [PMID: 20190789 DOI: 10.1038/cmi.2010.2]
24 **Kabir S**. The role of interleukin-17 in the Helicobacter pylori induced infection and immunity. *Helicobacter* 2011; **16**: 1-8 [PMID: 21241406 DOI: 10.1111/j.1523-5378.2010.00812.x]
25 **Malfertheiner P**. The intriguing relationship of Helicobacter pylori infection and acid secretion in peptic ulcer disease and gastric cancer. *Dig Dis* 2011; **29**: 459-464 [PMID: 22095010 DOI: 10.1159/000332213]
26 **Sonnenberg A**. Time trends of ulcer mortality in Europe. *Gastroenterology* 2007; **132**: 2320-2327 [PMID: 17570207 DOI: 10.1053/j.gastro.2007.03.108]
27 **Zapata-Colindres JC**, Zepeda-Gómez S, Montaño-Loza A, Vázquez-Ballesteros E, de Jesús Villalobos J, Valdovinos-Andraca F. The association of Helicobacter pylori infection and nonsteroidal anti-inflammatory drugs in peptic ulcer disease. *Can J Gastroenterol* 2006; **20**: 277-280 [PMID: 16609757]
28 **Hagymási K**, Tulassay Z. [Peptic ulcer: facts and questions -- 2010]. *Orv Hetil* 2010; **151**: 1054-1061 [PMID: 20558352 DOI: 10.1556/OH.2010.28892]
29 **de Martel C**, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, Plummer M. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol* 2012; **13**: 607-615 [PMID: 22575588 DOI: 10.1016/S1470-2045(12)70137-7]
30 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789 [PMID: 11556297 DOI: 10.1056/NEJMoa001999]
31 **Venkateshwari A**, Krishnaveni D, Venugopal S, Shashikumar P, Vidyasagar A, Jyothy A. Helicobacter pylori infection in relation to gastric cancer progression. *Indian J Cancer* 2011; **48**: 94-98 [PMID: 21248438 DOI: 10.4103/0019-509X.75840]
32 **Pandey R**, Misra V, Misra SP, Dwivedi M, Kumar A, Tiwari BK. Helicobacter pylori and gastric cancer. *Asian Pac J Cancer Prev* 2010; **11**: 583-588 [PMID: 21039020]
33 **Hu Y**, Fang JY, Xiao SD. Can the incidence of gastric cancer be reduced in the new century? *J Dig Dis* 2013; **14**: 11-15 [PMID: 23134264 DOI: 10.1111/j.1751-2980.2012.00647.x]
34 **Correa P**, Piazuelo MB. The gastric precancerous cascade. *J Dig Dis* 2012; **13**: 2-9 [PMID: 22188910 DOI: 10.1111/j.1751-2980.2011.00550.x]
35 **Wang F**, Meng W, Wang B, Qiao L. Helicobacter pylori-induced gastric inflammation and gastric cancer. *Cancer Lett* 2014; **345**: 196-202 [PMID: 23981572 DOI: 10.1016/j.canlet.2013.08.016]
36 **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; China Gastric Cancer Study Group. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004; **291**: 187-194 [PMID: 14722144 DOI: 10.1001/jama.291.2.187]
37 **Mera R**, Fontham ET, Bravo LE, Bravo JC, Piazuelo MB, Camargo MC, Correa P. Long term follow up of patients treated for Helicobacter pylori infection. *Gut* 2005; **54**: 1536-1540 [PMID: 15985559 DOI: 10.1136/gut.2005.072009]
38 **Farinati F**, Cardin R, Della Libera G, Herszenyi L, Marafin C, Molari A, Plebani M, Rugge M, Naccarato R. The role of anti-oxidants in the chemoprevention of gastric cancer. *Eur J Cancer Prev* 1994; **3** Suppl 2: 93-97 [PMID: 7735055 DOI: 10.1097/00008469-199412002-00017]
39 **Tulassay Z**, Stolte M, Engstrand L, Butruk E, Malfertheiner P, Dítê P, Tchernev K, Wong BC, Gottlow M, Eklund S, Wrangstadh M, Herszényi L, Nagy P. Twelve-month endoscopic and histological analysis following proton-pump inhibitor-based triple therapy in Helicobacter pylori-positive patients with gastric ulcers. *Scand J Gastroenterol* 2010; **45**: 1048-1058 [PMID: 20509752 DOI: 10.3109/00365520903575737]
40 **Ferreira AC**, Isomoto H, Moriyama M, Fujioka T, Machado JC, Yamaoka Y. Helicobacter and gastric malignancies. *Helicobacter* 2008; **13** Suppl 1: 28-34 [PMID: 18783519 DOI: 10.1111/j.1523-5378.2008.00633.x]
41 **Asenjo LM**, Gisbert JP. Prevalence of Helicobacter pylori infection in gastric MALT lymphoma: a systematic review. *Rev Esp Enferm Dig* 2007; **99**: 398-404 [PMID: 17973584 DOI: 10.4321/S1130-01082007000700006]
42 **Kusters JG**, van Vliet AH, Kuipers EJ. Pathogenesis of Helicobacter pylori infection. *Clin Microbiol Rev* 2006; **19**: 449-490 [PMID: 16847081 DOI: 10.1128/CMR.00054-05]
43 **Zullo A**, Hassan C, Cristofari F, Andriani A, De Francesco V, Ierardi E, Tomao S, Stolte M, Morini S, Vaira D. Effects of Helicobacter pylori eradication on early stage gastric mucosa-associated lymphoid tissue lymphoma. *Clin Gastroenterol Hepatol* 2010; **8**: 105-110 [PMID: 19631287 DOI: 10.1016/j.cgh.2009.07.017]
44 **Wündisch T**, Dieckhoff P, Greene B, Thiede C, Wilhelm C, Stolte M, Neubauer A. Second cancers and residual disease in patients treated for gastric mucosa-associated lymphoid tissue lymphoma by Helicobacter pylori eradication and followed for 10 years. *Gastroenterology* 2012; **143**: 936-942; quiz e13-14 [PMID: 22750463 DOI: 10.1053/j.gastro.2012.06.035]
45 **Singh K**, Ghoshal UC. Causal role of Helicobacter pylori infection in gastric cancer: an Asian enigma. *World J Gastroenterol* 2006; **12**: 1346-1351 [PMID: 16552799 DOI: 10.3748/wjg.v12.i9.1346]
46 **Suzuki R**, Shiota S, Yamaoka Y. Molecular epidemiology, population genetics, and pathogenic role of Helicobacter pylori. *Infect Genet Evol* 2012; **12**: 203-213 [PMID: 22197766 DOI: 10.1016/j.meegid.2011.12.002]
47 **Hwang IR**, Kodama T, Kikuchi S, Sakai K, Peterson LE, Graham DY, Yamaoka Y. Effect of interleukin 1 polymorphisms on gastric mucosal interleukin 1beta production in Helicobacter pylori infection. *Gastroenterology* 2002; **123**: 1793-1803 [PMID: 12454835 DOI: 10.1053/gast.2002.37043]
48 **Shanks AM**, El-Omar EM. Helicobacter pylori infection, host genetics and gastric cancer. *J Dig Dis* 2009; **10**: 157-164 [PMID: 19659782 DOI: 10.1111/j.1751-2980.2009.00380.x]
49 **Machado JC**, Figueiredo C, Canedo P, Pharoah P, Carvalho R, Nabais S, Castro Alves C, Campos ML, Van Doorn LJ, Caldas C, Seruca R, Carneiro F, Sobrinho-Simões M. A proinflammatory genetic profile increases the risk for chronic atrophic gastritis and gastric carcinoma. *Gastroenterology* 2003; **125**: 364-371 [PMID: 12891537 DOI: 10.1016/S0016-5085(03)00899-0]
50 **El-Omar EM**, Rabkin CS, Gammon MD, Vaughan TL, Risch HA, Schoenberg JB, Stanford JL, Mayne ST, Goedert J, Blot WJ, Fraumeni JF, Chow WH. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. *Gastroenterology* 2003; **124**: 1193-1201 [PMID: 12730860 DOI: 10.1016/S0016-5085(03)00157-4]
51 **Nagini S**. Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. *World J Gastrointest Oncol* 2012; **4**: 156-169 [PMID: 22844547 DOI: 10.4251/wjgo.v4.i7.156]
52 **Wang XQ**, Terry PD, Yan H. Review of salt consumption and stomach cancer risk: epidemiological and biological evidence. *World J Gastroenterol* 2009; **15**: 2204-2213 [PMID: 19437559 DOI: 10.3748/wjg.15.2204]
53 **Loh JT**, Torres VJ, Cover TL. Regulation of Helicobacter pylori cagA expression in response to salt. *Cancer Res* 2007; **67**: 4709-4715 [PMID: 17510398 DOI: 10.1158/0008-5472.CAN-06-4746]
54 **Ek C**, Whary MT, Ihrig M, Bravo LE, Correa P, Fox JG. Serologic evidence that ascaris and toxoplasma infections impact inflammatory responses to Helicobacter pylori in Colombians. *Helicobacter* 2012; **17**: 107-115 [PMID: 22404440 DOI: 10.1111/j.1523-5378.2011.00916.x]
55 **Tsugane S**, Sasazuki S. Diet and the risk of gastric cancer:

review of epidemiological evidence. *Gastric Cancer* 2007; **10**: 75-83 [PMID: 17577615 DOI: 10.1007/s10120-007-0420-0]
56 **Ma JL**, Zhang L, Brown LM, Li JY, Shen L, Pan KF, Liu WD, Hu Y, Han ZX, Crystal-Mansour S, Pee D, Blot WJ, Fraumeni JF, You WC, Gail MH. Fifteen-year effects of Helicobacter pylori, garlic, and vitamin treatments on gastric cancer incidence and mortality. *J Natl Cancer Inst* 2012; **104**: 488-492 [PMID: 22271764 DOI: 10.1093/jnci/djs003]
57 **Zhang ZW**, Farthing MJ. The roles of vitamin C in Helicobacter pylori associated gastric carcinogenesis. *Chin J Dig Dis* 2005; **6**: 53-58 [PMID: 15904421 DOI: 10.1111/j.1443-9573.2005.00194.x]
58 **Shikata K**, Doi Y, Yonemoto K, Arima H, Ninomiya T, Kubo M, Tanizaki Y, Matsumoto T, Iida M, Kiyohara Y. Population-based prospective study of the combined influence of cigarette smoking and Helicobacter pylori infection on gastric cancer incidence: the Hisayama Study. *Am J Epidemiol* 2008; **168**: 1409-1415 [PMID: 18945691 DOI: 10.1093/aje/kwn276]
59 **Raderer M**, Wrba F, Kornek G, Maca T, Koller DY, Weinlaender G, Hejna M, Scheithauer W. Association between Helicobacter pylori infection and pancreatic cancer. *Oncology* 1998; **55**: 16-19 [PMID: 9428370 DOI: 10.1159/000011830]
60 **Stolzenberg-Solomon RZ**, Blaser MJ, Limburg PJ, Perez-Perez G, Taylor PR, Virtamo J, Albanes D. Helicobacter pylori seropositivity as a risk factor for pancreatic cancer. *J Natl Cancer Inst* 2001; **93**: 937-941 [PMID: 11416115 DOI: 10.1093/jnci/93.12.937]
61 **Trikudanathan G**, Philip A, Dasanu CA, Baker WL. Association between Helicobacter pylori infection and pancreatic cancer. A cumulative meta-analysis. *JOP* 2011; **12**: 26-31 [PMID: 21206097]
62 **Michaud DS**. Role of bacterial infections in pancreatic cancer. *Carcinogenesis* 2013; **34**: 2193-2197 [PMID: 23843038 DOI: 10.1093/carcin/bgt249]
63 **Jesnowski R**, Isaksson B, Möhrcke C, Bertsch C, Bulajic M, Schneider-Brachert W, Klöppel G, Lowenfels AB, Maisonneuve P, Löhr JM. Helicobacter pylori in autoimmune pancreatitis and pancreatic carcinoma. *Pancreatology* 2010; **10**: 462-466 [PMID: 20720447 DOI: 10.1159/000264677]
64 **Risch HA**. Etiology of pancreatic cancer, with a hypothesis concerning the role of N-nitroso compounds and excess gastric acidity. *J Natl Cancer Inst* 2003; **95**: 948-960 [PMID: 12837831 DOI: 10.1093/jnci/95.13.948]
65 **Risch HA**. Pancreatic cancer: Helicobacter pylori colonization, N-nitrosamine exposures, and ABO blood group. *Mol Carcinog* 2012; **51**: 109-118 [PMID: 22162235 DOI: 10.1002/mc.20826]
66 **Howatson AG**, Carter DC. Pancreatic carcinogenesis: effect of secretin in the hamster- nitrosamine model. *J Natl Cancer Inst* 1987; **78**: 101-105 [PMID: 3467121]
67 **Annibale B**, Capurso G, Delle Fave G. Consequences of Helicobacter pylori infection on the absorption of micronutrients. *Dig Liver Dis* 2002; **34** Suppl 2: S72-S77 [PMID: 12408446 DOI: 10.1016/S1590-8658(02)80170-0]
68 **Machida-Montani A**, Sasazuki S, Inoue M, Natsukawa S, Shaura K, Koizumi Y, Kasuga Y, Hanaoka T, Tsugane S. Atrophic gastritis, Helicobacter pylori, and colorectal cancer risk: a case-control study. *Helicobacter* 2007; **12**: 328-332 [PMID: 17669106 DOI: 10.1111/j.1523-5378.2007.00513.x]
69 **Lin YL**, Chiang JK, Lin SM, Tseng CE. Helicobacter pylori infection concomitant with metabolic syndrome further increase risk of colorectal adenomas. *World J Gastroenterol* 2010; **16**: 3841-3846 [PMID: 20698048 DOI: 10.3748/wjg.v16.i30.3841]
70 **Wu Q**, Yang ZP, Xu P, Gao LC, Fan DM. Association between Helicobacter pylori infection and the risk of colorectal neoplasia: a systematic review and meta-analysis. *Colorectal Dis* 2013; **15**: e352-e364 [PMID: 23672575 DOI: 10.1111/codi.12284]
71 **Jones M**, Helliwell P, Pritchard C, Tharakan J, Mathew J. Helicobacter pylori in colorectal neoplasms: is there an aetiological relationship? *World J Surg Oncol* 2007; **5**: 51 [PMID: 17498313 DOI: 10.1186/1477-7819-5-51]
72 **Kountouras J**, Kapetanakis N, Zavos C, Romiopoulos I. Impact of Helicobacter pylori infection on normal colorectal mucosa, adenomatous polyps and adenocarcinoma sequence. *Colorectal Dis* 2014; **16**: 390-391 [PMID: 23869417 DOI: 10.1111/codi.12356]
73 **Nam KW**, Baeg MK, Kwon JH, Cho SH, Na SJ, Choi MG. Helicobacter pylori seropositivity is positively associated with colorectal neoplasms. *Korean J Gastroenterol* 2013; **61**: 259-264 [PMID: 23756667 DOI: 10.4166/kjg.2013.61.5.259]
74 **Visek WJ**. Diet and cell growth modulation by ammonia. *Am J Clin Nutr* 1978; **31**: S216-S220 [PMID: 707376]
75 **Clinton SK**, Bostwick DG, Olson LM, Mangian HJ, Visek WJ. Effects of ammonium acetate and sodium cholate on N-methyl-N′-nitro-N-nitrosoguanidine-induced colon carcinogenesis of rats. *Cancer Res* 1988; **48**: 3035-3039 [PMID: 3365693]
76 **Cavallo P**, Cianciulli A, Mitolo V, Panaro MA. Lipopolysaccharide (LPS) of helicobacter modulates cellular DNA repair systems in intestinal cells. *Clin Exp Med* 2011; **11**: 171-179 [PMID: 21069418 DOI: 10.1007/s10238-010-0118-1]
77 **Inoue I**, Mukoubayashi C, Yoshimura N, Niwa T, Deguchi H, Watanabe M, Enomoto S, Maekita T, Ueda K, Iguchi M, Yanaoka K, Tamai H, Arii K, Oka M, Fujishiro M, Takeshita T, Iwane M, Mohara O, Ichinose M. Elevated risk of colorectal adenoma with Helicobacter pylori-related chronic gastritis: a population-based case-control study. *Int J Cancer* 2011; **129**: 2704-2711 [PMID: 21225622 DOI: 10.1002/ijc.25931]
78 **Aly A**, Shulkes A, Baldwin GS. Gastrins, cholecystokinins and gastrointestinal cancer. *Biochim Biophys Acta* 2004; **1704**: 1-10 [PMID: 15238241 DOI: 10.1016/j.bbcan.2004.01.004]
79 **Yu H**, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. *J Natl Cancer Inst* 2000; **92**: 1472-1489 [PMID: 10995803 DOI: 10.1093/jnci/92.18.1472]
80 **Eckel RH**, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005; **365**: 1415-1428 [PMID: 15836891 DOI: 10.1016/S0140.-6736(05)66378-7]
81 **Hill MJ**. Bile flow and colon cancer. *Mutat Res* 1990; **238**: 313-320 [PMID: 2188127 DOI: 10.1016/0165.-1110(90)90023-5]
82 **Xiong LJ**, Tong Y, Wang ZL, Mao M. Is Helicobacter pylori infection associated with Henoch-Schonlein purpura in Chinese children? a meta-analysis. *World J Pediatr* 2012; **8**: 301-308 [PMID: 23151856 DOI: 10.1007/s12519-012-0373-1]
83 **Hernando-Harder AC**, Booken N, Goerdt S, Singer MV, Harder H. Helicobacter pylori infection and dermatologic diseases. *Eur J Dermatol* 2009; **19**: 431-444 [PMID: 19527988 DOI: 10.1684/ejd.2009.0739]
84 **Fock KM**, Katelaris P, Sugano K, Ang TL, Hunt R, Talley NJ, Lam SK, Xiao SD, Tan HJ, Wu CY, Jung HC, Hoang BH, Kachintorn U, Goh KL, Chiba T, Rani AA. Second Asia-Pacific Consensus Guidelines for Helicobacter pylori infection. *J Gastroenterol Hepatol* 2009; **24**: 1587-1600 [PMID: 19788600 DOI: 10.1111/j.1440-1746.2009.05982.x]
85 **Malfertheiner P**, Selgrad M, Bornschein J. Helicobacter pylori: clinical management. *Curr Opin Gastroenterol* 2012; **28**: 608-614 [PMID: 23010682 DOI: 10.1097/MOG.0b013e32835918a7]
86 **Rabelo-Gonçalves EM**, Sgardioli IC, Lopes-Cendes I, Escanhoela CA, Almeida JR, Zeitune JM. Improved detection of Helicobacter pylori DNA in formalin-fixed paraffin-embedded (FFPE) tissue of patients with hepatocellular carcinoma using laser capture microdissection (LCM). *Helicobacter* 2013; **18**: 244-245 [PMID: 23350684 DOI: 10.1111/hel.12040]
87 **Esmat G**, El-Bendary M, Zakarya S, Ela MA, Zalata K. Role of Helicobacter pylori in patients with HCV-related chronic hepatitis and cirrhosis with or without hepatocellular carcinoma: possible association with disease progression. *J Viral Hepat* 2012; **19**: 473-479 [PMID: 22676359 DOI: 10.1111/

j.1365-2893.2011.01567.x]
88 **Tu QV**, Okoli AS, Kovach Z, Mendz GL. Hepatocellular carcinoma: prevalence and molecular pathogenesis of Helicobacter spp. *Future Microbiol* 2009; **4**: 1283-1301 [PMID: 19995189 DOI: 10.2217/fmb.09.90]
89 **Xuan SY**, Xin YN, Chen AJ, Dong QJ, Qiang X, Li N, Zheng MH, Guan HS. Association between the presence of H pylori in the liver and hepatocellular carcinoma: a meta-analysis. *World J Gastroenterol* 2008; **14**: 307-312 [PMID: 18186573 DOI: 10.3748/wjg.14.307]
90 **Abdel-Hady H**, Zaki A, Badra G, Lotfy M, Selmi C, Giorgini A, El-Sayed M, Badr R. Helicobacter pylori infection in hepatic encephalopathy: Relationship to plasma endotoxins and blood ammonia. *Hepatol Res* 2007; **37**: 1026-1033 [PMID: 17610507 DOI: 10.1111/j.1872-034X.2007.00146.x]
91 **Liu X**, Liang J, Li G. Lipopolysaccharide promotes adhesion and invasion of hepatoma cell lines HepG2 and HepG2.2.15. *Mol Biol Rep* 2010; **37**: 2235-2239 [PMID: 19680784 DOI: 10.1007/s11033-009-9710-4]
92 **Zhuo XL**, Wang Y, Zhuo WL, Zhang XY. Possible association of Helicobacter pylori infection with laryngeal cancer risk: an evidence-based meta-analysis. *Arch Med Res* 2008; **39**: 625-628 [PMID: 18662596 DOI: 10.1016/j.arcmed.2008.04.008]
93 **Burduk PK**. Association between infection of virulence cagA gene Helicobacter pylori and laryngeal squamous cell carcinoma. *Med Sci Monit* 2013; **19**: 584-591 [PMID: 23860397 DOI: 10.12659/MSM.889011]
94 **Koshiol J**, Flores R, Lam TK, Taylor PR, Weinstein SJ, Virtamo J, Albanes D, Perez-Perez G, Caporaso NE, Blaser MJ. Helicobacter pylori seropositivity and risk of lung cancer. *PLoS One* 2012; **7**: e32106 [PMID: 22384154 DOI: 10.1371/journal.pone.0032106]
95 **Deng B**, Li Y, Zhang Y, Bai L, Yang P. Helicobacter pylori infection and lung cancer: a review of an emerging hypothesis. *Carcinogenesis* 2013; **34**: 1189-1195 [PMID: 23568955 DOI: 10.1093/carcin/bgt114]
96 **Chen Y**, Segers S, Blaser MJ. Association between Helicobacter pylori and mortality in the NHANES III study. *Gut* 2013; **62**: 1262-1269 [PMID: 23303440 DOI: 10.1136/gutjnl-2012-303018]
97 **Moss SF**. The carcinogenic effect of H. pylori on the gastric epithelial cell. *J Physiol Pharmacol* 1999; **50**: 847-856 [PMID: 10695564]
98 **Zhuo WL**, Zhu B, Xiang ZL, Zhuo XL, Cai L, Chen ZT. Assessment of the relationship between Helicobacter pylori and lung cancer: a meta-analysis. *Arch Med Res* 2009; **40**: 406-410 [PMID: 19766906 DOI: 10.1016/j.arcmed.2009.05.002]
99 **Gunji T**, Matsuhashi N, Sato H, Fujibayashi K, Okumura M, Sasabe N, Urabe A. Helicobacter pylori infection is significantly associated with metabolic syndrome in the Japanese population. *Am J Gastroenterol* 2008; **103**: 3005-3010 [PMID: 19086952 DOI: 10.1111/j.1572-0241.2008.02151.x]
100 **Gunji T**, Matsuhashi N, Sato H, Fujibayashi K, Okumura M, Sasabe N, Urabe A. Helicobacter pylori infection significantly increases insulin resistance in the asymptomatic Japanese population. *Helicobacter* 2009; **14**: 144-150 [PMID: 19751440 DOI: 10.1111/j.1523-5378.2009.00705.x]
101 **Gen R**, Demir M, Ataseven H. Effect of Helicobacter pylori eradication on insulin resistance, serum lipids and low-grade inflammation. *South Med J* 2010; **103**: 190-196 [PMID: 20134372 DOI: 10.1097/SMJ.0b013e3181cf373f]
102 **Gillum RF**. Infection with Helicobacter pylori, coronary heart disease, cardiovascular risk factors, and systemic inflammation: the Third National Health and Nutrition Examination Survey. *J Natl Med Assoc* 2004; **96**: 1470-1476 [PMID: 15586651]
103 **Naja F**, Nasreddine L, Hwalla N, Moghames P, Shoaib H, Fatfat M, Sibai A, Gali-Muhtasib H. Association of H. pylori infection with insulin resistance and metabolic syndrome among Lebanese adults. *Helicobacter* 2012; **17**: 444-451 [PMID: 23066847 DOI: 10.1111/j.1523-5378.2012.00970.x]
104 **Ando T**, Ishikawa T, Takagi T, Imamoto E, Kishimoto E, Okajima A, Uchiyama K, Handa O, Yagi N, Kokura S, Naito Y, Mizuno S, Asakawa A, Inui A, Yoshikawa T. Impact of Helicobacter pylori eradication on circulating adiponectin in humans. *Helicobacter* 2013; **18**: 158-164 [PMID: 23167259 DOI: 10.1111/hel.12028]
105 **Polyzos SA**, Kountouras J, Zavos C, Deretzi G. The association between Helicobacter pylori infection and insulin resistance: a systematic review. *Helicobacter* 2011; **16**: 79-88 [PMID: 21435084 DOI: 10.1111/j.1523-5378.2011.00822.x]
106 **Albaker WI**. Helicobacter pylori infection and its relationship to metabolic syndrome: is it a myth or fact? *Saudi J Gastroenterol* 2011; **17**: 165-169 [PMID: 21546717 DOI: 10.4103/1319-3767.80377]
107 **Eshraghian A**, Eshraghian H, Ranjbar Omrani G. Insulin resistance and metabolic syndrome: is Helicobacter pylori criminal? *Minerva Gastroenterol Dietol* 2011; **57**: 379-385 [PMID: 22105726]
108 **Tan HJ**, Goh KL. Extragastrointestinal manifestations of Helicobacter pylori infection: facts or myth? A critical review. *J Dig Dis* 2012; **13**: 342-349 [PMID: 22713083 DOI: 10.1111/j.1751-2980.2012.00599.x]
109 **Christodoulou DK**, Milionis HJ, Pappa P, Katsanos KH, Sigounas D, Florentin M, Elisaf M, Tsianos EV. Association of Helicobacter pylori infection with cardiovascular disease--is it just a myth? *Eur J Intern Med* 2011; **22**: 191-194 [PMID: 21402252 DOI: 10.1016/j.ejim.2010.11.010]
110 **Schöttker B**, Adamu MA, Weck MN, Müller H, Brenner H. Helicobacter pylori infection, chronic atrophic gastritis and major cardiovascular events: a population-based cohort study. *Atherosclerosis* 2012; **220**: 569-574 [PMID: 22189198 DOI: 10.1016/j.atherosclerosis.2011.11.029]
111 **Suzuki H**, Franceschi F, Nishizawa T, Gasbarrini A. Extragastric manifestations of Helicobacter pylori infection. *Helicobacter* 2011; **16** Suppl 1: 65-69 [PMID: 21896088 DOI: 10.1111/j.1523-5378.2011.00883.x]
112 **Danesh J**, Peto R. Risk factors for coronary heart disease and infection with Helicobacter pylori: meta-analysis of 18 studies. *BMJ* 1998; **316**: 1130-1132 [PMID: 9552950 DOI: 10.1136/bmj.316.7138.1130]
113 **Vahdat K**, Pourbehi MR, Ostovar A, Hadavand F, Bolkheir A, Assadi M, Farrokhnia M, Nabipour I. Association of pathogen burden and hypertension: the Persian Gulf Healthy Heart Study. *Am J Hypertens* 2013; **26**: 1140-1147 [PMID: 23744497 DOI: 10.1093/ajh/hpt083]
114 **Fagoonee S**, De Angelis C, Elia C, Silvano S, Oliaro E, Rizzetto M, Pellicano R. Potential link between Helicobacter pylori and ischemic heart disease: does the bacterium elicit thrombosis? *Minerva Med* 2010; **101**: 121-125 [PMID: 20467411]
115 **Yu T**, Wu D, Zhao XY. Infection and eradication of Helicobacter Pylorus affecting etiology and curative effect of idiopathic thrombocytopenic purpura: a META analysis. *Zhongguo Shiyanxue Yexue Zazhi* 2011; **19**: 1255-1259 [PMID: 22040983]
116 **Franchini M**, Veneri D. Helicobacter pylori-associated immune thrombocytopenia. *Platelets* 2006; **17**: 71-77 [PMID: 16421007 DOI: 10.1080/09537100500438057]
117 **Hasni SA**. Role of Helicobacter pylori infection in autoimmune diseases. *Curr Opin Rheumatol* 2012; **24**: 429-434 [PMID: 22617822 DOI: 10.1097/BOR.0b013e3283542d0b]
118 **Li Q**, Lin X, Wu Z, He L, Wang W, Cao Q, Zhang J. Immunohistochemistry analysis of Helicobacter pylori antigen in renal biopsy specimens from patients with glomerulonephritis. *Saudi J Kidney Dis Transpl* 2013; **24**: 751-758 [PMID: 23816725 DOI: 10.4103/1319-2442.113871]
119 **Muhsen K**, Cohen D. Helicobacter pylori infection and iron stores: a systematic review and meta-analysis. *Helicobacter* 2008; **13**: 323-340 [PMID: 19250507 DOI: 10.1111/j.1523-5378.2008.00617.x]

120 **Qu XH**, Huang XL, Xiong P, Zhu CY, Huang YL, Lu LG, Sun X, Rong L, Zhong L, Sun DY, Lin H, Cai MC, Chen ZW, Hu B, Wu LM, Jiang YB, Yan WL. Does Helicobacter pylori infection play a role in iron deficiency anemia? A meta-analysis. *World J Gastroenterol* 2010; **16**: 886-896 [PMID: 20143469 DOI: 10.3748/wjg.v16.i7.886]
121 **Zhang ZF**, Yang N, Zhao G, Zhu L, Zhu Y, Wang LX. Effect of Helicobacter pylori eradication on iron deficiency. *Chin Med J* (Engl) 2010; **123**: 1924-1930 [PMID: 20819579]
122 **Realdi G**, Dore MP, Fastame L. Extradigestive manifestations of Helicobacter pylori infection: fact and fiction. *Dig Dis Sci* 1999; **44**: 229-236 [PMID: 10063905 DOI: 10.1023/A:1026677728175]
123 **Ozkasap S**, Yarali N, Isik P, Bay A, Kara A, Tunc B. The role of prohepcidin in anemia due to Helicobacter pylori infection. *Pediatr Hematol Oncol* 2013; **30**: 425-431 [PMID: 23560993 DOI: 10.3109/08880018.2013.783144]
124 **Xie T**, Cui X, Zheng H, Chen D, He L, Jiang B. Meta-analysis: eradication of Helicobacter pylori infection is associated with the development of endoscopic gastroesophageal reflux disease. *Eur J Gastroenterol Hepatol* 2013; **25**: 1195-1205 [PMID: 23839160 DOI: 10.1097/MEG.0b013e328363e2c7]
125 **El-Omar EM**, Oien K, El-Nujumi A, Gillen D, Wirz A, Dahill S, Williams C, Ardill JE, McColl KE. Helicobacter pylori infection and chronic gastric acid hyposecretion. *Gastroenterology* 1997; **113**: 15-24 [PMID: 9207257 DOI: 10.1016/S0016-5085(97)70075-1]
126 **Chow WH**, Blaser MJ, Blot WJ, Gammon MD, Vaughan TL, Risch HA, Perez-Perez GI, Schoenberg JB, Stanford JL, Rotterdam H, West AB, Fraumeni JF. An inverse relation between cagA+ strains of Helicobacter pylori infection and risk of esophageal and gastric cardia adenocarcinoma. *Cancer Res* 1998; **58**: 588-590 [PMID: 9485003]
127 **Rubenstein JH**, Inadomi JM, Scheiman J, Schoenfeld P, Appelman H, Zhang M, Metko V, Kao JY. Association between Helicobacter pylori and Barrett's esophagus, erosive esophagitis, and gastroesophageal reflux symptoms. *Clin Gastroenterol Hepatol* 2014; **12**: 239-245 [PMID: 23988686]
128 **Shahabi S**, Rasmi Y, Jazani NH, Hassan ZM. Protective effects of Helicobacter pylori against gastroesophageal reflux disease may be due to a neuroimmunological anti-inflammatory mechanism. *Immunol Cell Biol* 2008; **86**: 175-178 [PMID: 17923849 DOI: 10.1038/sj.icb.7100119]
129 **Zhuo X**, Zhang Y, Wang Y, Zhuo W, Zhu Y, Zhang X. Helicobacter pylori infection and oesophageal cancer risk: association studies via evidence-based meta-analyses. *Clin Oncol* (R Coll Radiol) 2008; **20**: 757-762 [PMID: 18793831 DOI: 10.1016/j.clon.2008.07.005]
130 **Wang Y**, Bi Y, Zhang L, Wang C. Is Helicobacter pylori infection associated with asthma risk? A meta-analysis based on 770 cases and 785 controls. *Int J Med Sci* 2012; **9**: 603-610 [PMID: 23028243 DOI: 10.7150/ijms.4970]
131 **Wang Q**, Yu C, Sun Y. The association between asthma and Helicobacter pylori: a meta-analysis. *Helicobacter* 2013; **18**: 41-53 [PMID: 23067334 DOI: 10.1111/hel.12012]
132 **Zhou X**, Wu J, Zhang G. Association between Helicobacter pylori and asthma: a meta-analysis. *Eur J Gastroenterol Hepatol* 2013; **25**: 460-468 [PMID: 23242126 DOI: 10.1097/MEG.0b013e32835c280a]
133 **Shiu J**, Czinn SJ, Kobayashi KS, Sun Y, Blanchard TG. IRAK-M expression limits dendritic cell activation and proinflammatory cytokine production in response to Helicobacter pylori. *PLoS One* 2013; **8**: e66914 [PMID: 23776703 DOI: 10.1371/journal.pone.0066914]
134 **Karimi A**, Fakhimi-Derakhshan K, Imanzadeh F, Rezaei M, Cavoshzadeh Z, Maham S. Helicobacter pylori infection and pediatric asthma. *Iran J Microbiol* 2013; **5**: 132-135 [PMID: 23825730]
135 **Bornschein J**, Malfertheiner P. Gastric carcinogenesis. *Langenbecks Arch Surg* 2011; **396**: 729-742 [PMID: 21611816 DOI: 10.1007/s00423-011-0810-y]
136 **Gonciarz M**, Włoch M, Gonciarz Z. Helicobacter pylori in liver diseases. *J Physiol Pharmacol* 2006; **57** Suppl 3: 155-161 [PMID: 17033113]
137 **Bohr UR**, Annibale B, Franceschi F, Roccarina D, Gasbarrini A. Extragastric manifestations of Helicobacter pylori infection -- other Helicobacters. *Helicobacter* 2007; **12** Suppl 1: 45-53 [PMID: 17727460 DOI: 10.1111/j.1523-5378.2007.00533.x]

P- Reviewers: Ali IKM, Bach H, Liu ZJ, Luo JC, Matar G, Nagahara H **S- Editor**: Ma YJ **L- Editor**: Rutherford A **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327