World Journal of Gastroenterology

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World J Gastroenterol 2017 March 7; 23(9): 1521-1540

DOI: 10.3748/wjg.v23.i9.1521

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

FRONTIER

Host pathogen interactions in *Helicobacter pylori* related gastric cancer

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Author contributions: Chmiela M designed, wrote and supervised the manuscript; Karwowska Z, Gonciarz W and Allushi B designed and wrote a part of the manuscript, Stączek P pre-reviewed the manuscript.

Conflict-of-interest statement: No potential conflicts of interest.

Manuscript source: Invited manuscript

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Received: August 24, 2016
Peer-review started: August 25, 2016
First decision: September 12, 2016
Revised: October 26, 2016
Accepted: February 16, 2017

Article in press: February 17, 2017
Published online: March 7, 2017

Abstract

Helicobacter pylori (*H. pylori*), discovered in 1982, is a microaerophilic, spiral-shaped gram-negative bacterium that is able to colonize the human stomach. Nearly half of the world's population is infected by this pathogen. Its ability to induce gastritis, peptic ulcers, gastric cancer and mucosa-associated lymphoid tissue lymphoma has been confirmed. The susceptibility of an individual to these clinical outcomes is multifactorial and depends on *H. pylori* virulence, environmental factors, the genetic susceptibility of the host and the reactivity of the host immune system. Despite the host immune response, *H. pylori* infection can be difficult to eradicate. *H. pylori* is categorized as a group I carcinogen since this bacterium is responsible for the highest rate of cancer-related deaths worldwide. Early detection of cancer can be lifesaving. The 5-year survival rate for gastric cancer patients diagnosed in the early stages is nearly 90%. Gastric cancer is asymptomatic in the early stages but always progresses over time and begins to cause symptoms when untreated. In 97% of stomach cancer cases, cancer cells metastasize to other organs. *H. pylori* infection is responsible for nearly 60% of the intestinal-type gastric cancer cases but also influences the development of diffuse gastric cancer. The host genetic susceptibility depends on polymorphisms of genes involved in *H. pylori*-related inflammation and the cytokine response of gastric epithelial and immune cells. *H. pylori* strains differ in their ability to induce a deleterious inflammatory response. *H. pylori*-driven cytokines accelerate the inflammatory response and promote malignancy. Chronic *H. pylori* infection induces genetic instability in gastric epithelial cells and affects the DNA damage repair systems. Therefore, *H. pylori* infection should always be considered a pro-cancerous factor.

Key words: *Helicobacter pylori*; Host susceptibility; Carcinogenesis; Bacterial diversity

Core tip: In 1994 *Helicobacter pylori* (*H. pylori*) was classified by the International Agency for Research of Cancer as a class I human carcinogen for gastric cancer. Nearly 60% of the intestinal type gastric cancers are associated with *H. pylori* infections. Cancer risk rises if strain possess virulence factors: CagA, VacA and BabA. These bacteria promotes gastric carcinogenesis by increased DNA damage, impairment of repair processes, induction of mitochondrial DNA and genomic mutations. Nearly 98% of mucosa associated lymphoid tissue lymphomas are *H. pylori* dependent. We discuss correlation between *H. pylori* and gastric cancer in the light of bacterial and host genetic variability.

Chmiela M, Karwowska Z, Gonciarz W, Allushi B, Stączek P. Host pathogen interactions in *Helicobacter pylori* related gastric cancer. *World J Gastroenterol* 2017; 23(9): 1521-1540 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i9/1521.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i9.1521

BIOGRAPHY

With a master degree on biology, microbiology as specialty, upon her PhD on Immunology in 1991, Magdalena Chmiela (Figure 1) was nominated in 2005 on the position of permanent Professor (medical microbiology, immunology) at the Faculty of Biology and Environmental Protection, University of Lodz, Poland. She is currently head of the Department of Immunology and Infectious Biology at the Institute of Microbiology, Biotechnology and Immunology. For more than 30 years her research concerns the immunology of infectious diseases including: immune processes regulating host-pathogen interactions, bacterial virulence factors that determine the course of infections, the use of microorganisms in the design and manufacture of biological components for potential therapeutic use, prevention and diagnostic. With particular attention she leads research on *Helicobacter pylori* (*H. pylori*) infections, which are responsible for gastric and duodenal ulcers and even stomach cancers. Work on this subject she began in 1992, being a member of the research team at the Department of Medical Microbiology Lund University in Sweden. She also conducts research about Campylobacter sp. With her experience she published numerous papers, review articles, coordinated and participated in a number of research projects and evaluated them as an expert. She is a member of the Scientific Council of the Institute of Medical Biology, Polish Academy of Sciences; editorial board member of the *World Journal of Gastroenterol* (2014-2017); member of American Society for Microbiology and Polish Society for Microbiology. She shares her professional activity between research work and academic professor activity.

Figure 1 Magdalena Chmiela, PhD, Professor, Department of Immunology and Infectious Biology, University of Lodz, Faculty of Biology and Environmental Protection, Lodz 90-237, Poland.

INTRODUCTION

The stomach is considered a hostile environment for microorganisms. The acidic pH and peristaltic movements of the stomach prevent colonization by pathogens. In 1982, Barry Marshall and Robin Warren revolutionized the concept of gastroduodenal diseases by the discovery of *H. pylori* and by proving that these gram-negative bacteria cause infections in humans due to colonization of the stomach. If the pathogen is not eradicated by the immune system of the host, it stimulates the development of chronic inflammation. The pathogen is a major agent in gastritis and peptic ulcers (PU), which were previously thought to be caused by stress and diet. Now it is known that *H. pylori* is also involved in the development of gastric cancer (GC).

The aim of this review is to present a brief overview of how *H. pylori* infection impacts tumorigenesis. Gastric adenocarcinoma has the second highest mortality rate in the world. Nearly half of the world's population is infected by *H. pylori.* Various structural components and soluble factors of *H. pylori* enable these microbes to colonize the stomach and induce an inflammatory response. Close contact with an infected person facilitates transmission of the pathogen by an oral-oral or oral-fecal route. Clinical outcomes that are linked with *H. pylori* infection include chronic inflammation of the gastric mucosa, gastric and duodenal ulcers (DUs) and GC. Although a correlation between the pathogen and carcinogenesis has been established, more studies are needed to understand specific mechanisms, the diversity of infectious agents, and the genetic susceptibility and immune profile of the host.

MICROBIOLOGICAL ASPECTS OF *H. PYLORI*

Primary bacteriological features

H. pylori is considered the most prevalent human pathogen, and its evolution appears to have been very effective since the bacterium has developed several strategies to cause infection[1]. *H. pylori* had escaped the attention of researchers until Barry Marshall and Robin Warren published data on the curved bacterium that colonizes the human stomach[2]. Substantial alterations have been made concerning the disease causation after intensive studies on *H. pylori*[3]. This pathogenic microorganism was first named *Campylobacter pyloridis*. It was only after facing important genotypic and phenotypic dissimilarities with other bacteria in the *Campylobacter* genus that a decision was made to create a new genus: *Helicobacter.* It is now commonly accepted that this gram-negative, microaerophilic, flagellated microorganism induces chronic active gastritis (asymptomatic or symptomatic), peptic ulcer disease and duodenal ulcers in humans; it is also related to GC[4,5].

Virulence factors

The colonization of epithelial cells of the stomach by *H. pylori* begins with the binding of these bacteria with epithelial cell receptors. Then the bacteria escape of host defense mechanisms, induce inflammatory responses, which allow acquisition of nutrients for successful replication[6]. Majour *H. pylori* adhesins belong to the family of proteins localized in outer membrain of bacterial cells. The blood group antigen-binding adhesin A (BabA) and sialic acid binding adhesin (SabA) are the most important adhesisns of *H. pylori*[7-11]. Also other OMPs, such as HopZ and OipA play a role of adhesins. It has been shown that OipA induces more intensive inflammatory response due to neutrophil infiltration and promotes the development of duodenal ulcer and gastric cancer[7]. Urease elevates the acidic pH of the stomach and unipolar flagella facilitate penetration of mucus[3]. The ability to glycosylate host cholesterol is crucial for the virulence and antibiotic resistance of *H. pylori*[12]. *H. pylori* lipopolysaccharide (LPS), due to its structural features, induces a poor immune response and helps the bacteria develop into a chronic infection[13-18]. *H. pylori* LPS may carry various human Lewis (Le)-like antigens, which may play a role in autoimmunity. Specifically, Le^x determinants in O antigen of *H. pylori* LPS may facilitate the adherence of bacterial cells to gastric epithelium. This process involves the binding of gastric receptor β-galactoside-binding lectin (galectin-3)[19-21]. The *H. pylori* outer membrane vesicles are an alternative vehicle for the distribution of bacterial virulence factors and antigens[22,23]. The major virulence factors of *H. pylori* are encoded by genes within the pathogenicity island (PAI). The cytotoxin-associated gene A (CagA) protein is one of the most important *H. pylori* virulence factors. CagA is encoded by the *cagA* gene and translocated to the host gastric epithelial cells through a type Ⅳ secretion system[24-28]. A correlation between the presence of CagA in *H. pylori* strains and more severe inflammatory responses and a higher risk of gastric cancer has been shown[26-29]. Other virulence proteins include vacuolating cytotoxin A (VacA), BabA and SabA[9,10,30,31]. VacA induces vacuolation of gastric epithelial cells as well as cell apoptosis and disrupts the gastric epithelial barrier function[28]. BabA and SabA are adhesins, and SabA is essential for nonopsonic activation of human neutrophils[9,7]. BabA interacts with the Le^b blood group antigen on epithelial cells, and the *babA2* gene is associated with DU and GC[10]. SabA is known to bind sialyl-dimeric-Le^x[8], as well as sialylated Le^a[9]. Malignant transformation is linked with pronounced expression of Le^a, sialylated Le^a and sialyl-dimeric-Le^x, however, knowledge about the role of SabA in tumorigenesis is still limited[9].

Immune system evasion strategies

Blaser (1993) proposed a model in which both the host and the parasite adapt to downregulate the inflammatory response to promote survival and to continue colonization of the niche[32-34]. Pathogen-associated molecular patterns (PAMPs) are various molecules of pathogenic microorganisms that in normal conditions are recognized by pattern recognition receptors (PRRs) resulting in triggering of the inflammatory response. *H. pylori* possess several mechanisms that prevent their recognition *via* Toll-like receptors (TLRs): (1) changing and rearranging LPS and flagellin; and (2) molecular mimicry between human Lewis and ABO blood group antigens and bacterial compounds, which confuses immune cells and prevents recognition of the pathogen[21,35,36]. It has been shown that the *H. pylori* flagellin is not detected by specific PRRs, and it does not stimulate the production of interleukin (IL)-8. As a result, chemotaxis of immune cells to the site of infection and phagocytosis of *H. pylori* are diminished[37].

Prevention of phagocytic killing has been demonstrated to be more efficient due to delayed polymerization of actin and inhibition of phagosome and phagolysosome formation[28,38]. The primary host immune response mechanisms, such as phagocytosis and natural killer (NK) cell activity, have been found to be downregulated by *H. pylori* LPS[17,18,39,40]. Adaptive immunity is also targeted by *H. pylori* compounds[1,15,41,42]. They affect antigen presentation by inducing macrophage apoptosis and by diminishing dendritic cell (DC) and macrophage maturation[18,43]. The expression of programmed death 1 ligand-1 (B7-H1 integrin) on gastric epithelial cells modulates T cell trafficking during *H. pylori* infection. The function of B7-H1 is to inhibit effector T lymphocytes and stimulate DCs to increase secretion of the anti-inflammatory cytokine IL-10. B7-H1, by join-

ing programmed cell death receptor 1 on the surface of T cells, inhibits proliferation and differentiation of naïve T lymphocytes and promotes the activity of regulatory cells, which downregulates effector T lymphocytes. Regulatory T cells, which possess the ability to suppress anti-tumor and anti-infectious responses are identified on the basis of cluster differentiation (CD) markers and forkhead box P3 (FOXP3) as CD4(+)CD25(high) and FOXP3-positive. Enarsson *et al*[44] studied regulatory T lymphocytes in stomach tissue in *H. pylori* positive patients in terms of their activity and the expression of homing receptors. The increased number of regulatory T cells has been detected in gastric tissue of patients with gastric tumor *vs* non-tumor patients. Regulatory T lymphocytes suppressed *H. pylori*-induced T cell proliferation and interferon (IFN)-γ production. Furthermore, these regulatory T lymphocytes expressed increased levels of l-selectin and C-C chemokine receptor 4, than the cells lacking regulatory function. These receptors may be involved in the infiltration of regulatory lymphocytes specific to *H. pylori* antigens present in gastric tissue in *H. pylori* infected individuals. However, low activity of T regulatory cells may promote the maintenance of the infection and potentially the propagation of tumor cells[45]. The suppression of the activity of memory T lymphocytes, which enables a chronic infection, has been confirmed by other study groups[45-48]. The role of regulatory T lymphocytes can be related to the inhibition of the inflammatory response driven by IL-17 delivered by T helper (Th) 17 lymphocytes[49-52].

Different studies have shown that humoral response against *H. pylori* is less essential in the defense against this pathogen.The study on mice lacking B lymphocytes showed that gastritis, which developed in animals immunized with prophylactic vaccine was not related to B-cells. The response was similar to that of non immunized mice[53,54]. It can be concluded that antibody responses may not promote protection. However, a correlation between high levels of serum anti-*H. pylori* IgG and IgA and the development of gastritis, duodenal ulcers and gastric cancer has been shown[1].

PATHOGENIC ACTIVITY OF *H. PYLORI* IN THE HOST ORGANISM

Epidemiology

There is an inverse association between socioeconomic status and the rate of infection[54]. Analyses have been conducted to test whether animals or water can be sources of *H. pylori* infection. Only a few of the animal case studies showed positive results, leading to the conclusion that the infection cycle might include humans, the environment and animals. However, the water case studies failed to support the hypothesis that water is an environmental reservoir of *H. pylori*[55]. The principal method of spreading *H. pylori* infection is intrapersonal transmission. This has been confirmed by the high percentage of infections that are spread between close relatives, especially between a mother and her children[56].

Clinical complications

The clinical aspects of *H. pylori* infection vary from gastritis and peptic ulcers to gastric cancer. It has been suggested that the pathogen might also be associated with several extragastric diseases. Shortly after initial infection of the host, acute gastritis develops that is related to hypochlorhydria and to the loss of acid secretion. Acute gastritis does not last long, but in the majority of subjects, the immune response is unable to eradicate the infection, and as a consequence, chronic gastritis is induced. According to various studies, half of the world's population may suffer from chronic gastritis, which can be manifested in one of three forms: (1) antral-predominant; (2) corpus-predominant; and (3) diffuse. These pathologies lead to different consequences, which they favorably induce. Specifically, antral-predominant gastritis promotes duodenal ulcers whereas corpus-predominant gastritis promotes gastric ulcers, which may lead to metaplasia and adenocarcinoma; and diffuse gastritis is related to reduced acid secretion in the stomach[57-59]. In general *H. pylori* infections are responsible for 95% of duodenal ulcer cases and 85% of gastric ulcers. Nonsteroidal anti-inflammatory drugs are responsible for the cases that are not related to pathogen-induced inflammation[3]. Extragastric diseases potentially related to *H. pylori* include idiopathic thrombocytopenic purpura and iron deficiency anemia[60-66]. The influence of pathogen-induced inflammation has also been considered in several dermatological disorders, diabetes and cardiovascular, and pulmonary disease[67-76]. The connection between *H. pylori*-induced inflammation and cardiovascular disease was reported in 1994 by Mendall *et al*[77], and this work was then followed by many other studies[78-86]. However, the association between *H. pylori* infection and extragastric disease remains unclear. Therefore, the recommendation for *H. pylori* treatment is irrelevant[3]. According to recent data, *H. pylori* infection might facilitate the onset of hepatic encephalopathy[87]. The theory of *H. pylori* influence in diabetes is very recent. Specifically, $CagA^+$ strains are thought to enhance the risk of diabetic complications[88-92]. There is no doubt about the beneficial effect of the infection against endoscopic gastroesophageal reflux disease[93-95]. However, *H. pylori* infection may potentially prevent the development of adenocarcinoma of esophagus[96]. Based on a case-control study, infection with *H. pylori*, particularly the $CagA^+$ strain, has been found to be inversely associated with Barrett's esophagus[97]. *H. pylori* infection likely has a beneficial role in maturation of the immune system in the early stages of life

and prevents asthma development in the future[98-103]. The most dangerous clinical aspects of *H. pylori* are gastric cancer[29,48,104-108] and mucosa-associated lymphoid tissue (MALT) lymphoma[109-111]. The role of *H. pylori* in destruction of epithelial cell nuclei and mitochondrial DNA has been confirmed. This mutagenic effect is in part related to downregulation of the expression, as well as the activity, of DNA repair pathways. Machado *et al*[112] demonstrated that infection of gastric adenocarcinoma cells with *H. pylori* induced mutations in mitochondrial DNA and decreased the DNA content. The increased frequency of mutations in mitochondrial DNA was related to diminished effectiveness of DNA repair mechanisms. They showed that apurinic/apyrimidinic (AP) endonuclease-1 and Y-box-binding protein 1 mitochondrial base excision repair and mismatch repair systems are involved in DNA repair during *H. pylori* infection[112].

ROLE OF *H. PYLORI* IN TUMORIGENESIS

From carcinogenesis to gastric cancer

Accumulation of numerous mutations in DNA of gastric epithelial cells, resulting in activation of oncogens or inactivation of tumor suppressor genes promotes the development of gastric cancer[113,114].

Nearly 120 years ago, the first gastrectomy was performed to treat gastric cancer. Since then, tumor resection in the stomach has been the standard method of treatment. On average, only 15%-20% of patients live up to 5 years after resection. Patients diagnosed in the early stages of gastric cancer have a 5-year survival of nearly 90%[115,116]. Cancer in early stages can be surgically curable because of its local development. The advancement of gastric cancer is directly proportional to the involvement of regional and non-regional lymphoid nodes, as well as organ metastasis. If the cancer is scattered throughout the body, surgical methods that treat local cancer are not effective. In these cases, implementation of additional cytostatic and hormonal treatment is necessary. Approximately 97% of gastric cancer cases are linked with metastasis. Sarcomas and non-Hodgkin's lymphoma rarely occur. Every year, 670000 new cancer cases are registered around the world. Gastric cancer is two-times more frequent in men than in women. It usually occurs between the ages of 50 and 70, but lately, it is increasingly being detected in young people. Gastric cancer grows by contiguous extension (direct infiltration) to other organs, such as the pancreas, liver, transverse colon, duodenum and esophagus, as well as through the peritoneum to the recto-uterine Douglas pouch. Metastatic cancer spreads through the ovaries and lymphatic or blood vessels[115-117].

In 1965, Lauren described two histologically different stomach adenocarcinomas - diffuse and intestinal[118]. The diffuse type is considered an endemic cancer type. Diffuse adenocarcinoma affects mostly women and younger populations. The typical development area of the endemic type is the proximal portion of the stomach. It often coexists with the A blood group, which suggests a possible genetic basis for tumor formation. The intestinal type is related to preneoplastic changes, such as chronic atrophic gastritis and intestinal metaplasia of mucous membranes. This type concerns tumors in the peripheral part of the stomach. Intestinal adenocarcinoma is an epidemic type of cancer because it occurs in regions with a high risk of gastric cancer morbidity. It affects mostly men and older populations[116,118].

Gastric cancer as a consequence of H. pylori infection

The discovery of *H. pylori* confirmed that the etiology of chronic gastritis and the "precancerous cascade" resulting in cancer formation is associated with *H. pylori* infection[119]. Now, it is commonly accepted that *H. pylori* is a gastric cancer carcinogen since in 1994, *H. pylori* has been included by the International Agency for Research on Cancer to class I carcinogens[120]. Nearly 60% of intestinal-type gastric cancers are associated with such infections[121,122]. Over years, patients develop acute and then atrophic gastritis, followed by intestinal metaplasia, dysplasia and carcinoma. *H. pylori* infection also stimulates the development of diffuse type adenocarcinoma by causing pangastritis and rugal hyperplastic gastritis[123]. Cancer risk rises if virulence factors, such as CagA, VacA and BabA, are present in the *H. pylori* strain[28,29,124]. However, infection with *H. pylori* CagA$^+$ strains may potentially diminish the risk of adenocarcinoma of esophagus and gastric cardia[125]. There is an increasing interest on the role *H. pylori oipA* positive strains in the pathogenesis of gastric ulcer and cancer. When *oipA* is present, the functional "on" status of this gene was associated with increased risk of these diseases compared with gastritis and functional dyspepsia controls[7].

Environmental factors also stimulate the initiation of atrophic changes and decrease the secretion of hydrochloric acid. Elevated pH of the gastric juice facilitates bacterial colonization, causing further damage to epithelial cells. In addition, nitrates in foods are precursors of nitrosamines, which cause intestinal metaplasia and dysplasia (abnormal epithelial differentiation, in the form of improper development of the cells with the loss of ability to differentiate)[126,127].

Machado *et al*[128] have proposed three possible mechanisms of initiation of gastric cancer in response to *H. pylori* infection: damage of epithelial cell DNA combined with downregulation of repair processes, mitochondrial DNA mutations, and appearance of transient mutator phenotype. Park *et al*[129] showed that after eradication of *H. pylori* the expression of proteins consisting DNA mismatch repair (MMR) system was increased. This proved that gastric inflammation due

to *H. pylori* infection impairs MMR[129]. Kim *et al*[130] co-cultured gastric cell lines with *H. pylori* and the proteins (MutS and MutL) of DNA MMR, and examined quantitatively RNA levels. RNA of both proteins was reduced after exposure to *H. pylori*. Kidane *et al*[131] showed that damage of epithelial cell DNA due to oxidative stress, which increases during *H. pylori* infection is under control of base excision repair system and its effectiveness can be crucial for preventing genomic stability in response to *H. pylori* induced disorders. Toller *et al*[132] showed that *H. pylori* strains having the BabA adhesin are very effective in inducing double-strand breaks.

Biomarkers for detection of gastric cancer

Early detection of adenocarcinoma is essential. The 5-year survival rate for patients suffering from advanced stomach cancer is lower than 30%. Currently, endoscopic surveillance is the most applicable method for cancer detection. However, endoscopy has disadvantages, such as the invasiveness of the test and its high cost. It has been shown that appropriate biomarkers provide information about the diagnosis, prognosis and recurrence of cancer, as well as the optimal therapy[133]. Nevertheless, gastric cancer biomarkers such as pepsinogen, gastrin or *H. pylori* serology combined with pepsinogen (PG), do not indicate very precisely the state of the patient[134]. Pepsinogen is produced in the stomach as pepsinogen I (PGI) and pepsinogen II (PGII). The blood levels of PGI and PGI/PGII change during atrophic gastritis due to destruction of gastric glands. A research study involving approximately 300000 participants was performed in order to verify this observation. The results showed that out of 600 patients with atrophic gastritis, one developed stomach cancer. A PGI/PGII ratio within the normal range was very accurate negative predictor of an unhealthy stomach[135,136]. Gastrin is also considered a biomarker for gastric atrophy, but the connection between the biomarker and the disease is complex[137,138]. Gastrin is produced in the antrum of the stomach. In the case of antrum atrophic gastritis, the biomarker indicates a low gastrin level, but in the case of corpus atrophic gastritis, the gastrin level is increased. Generally, low and high levels of gastrin predict atrophic gastritis and gastric cancer, respectively. However, gastrin as a biomarker does not provide information about the cancer stage. Furthermore, combined tests for the detection of *H. pylori* and the PGI/PGII value also help to detect gastric cancer[139]. Patients with a seronegative *H. pylori* result and PG within the norm have very low rates of cancer susceptibility. The risk rises in cases of *H. pylori* seropositivity and low PGI/PGII values, suggesting the presence of gastric atrophy. However, negative *H. pylori* testing accompanied by low PGI/PGII indicates the manifestation of autoimmune metaplastic atrophic gastritis. This condition is linked with advanced grades of metaplasia in the stomach[54,134].

A novel group of biomarkers is microRNAs (miRNAs), which are nucleotides that modulate the expression of genes. miRNAs influence cell proliferation and differentiation and may act as oncogenes. Cancer-related miRNAs have been found in the blood stream and can be detected noninvasively. Levels of miRNAs in healthy patients provide information about cancer susceptibility. However, in patients with gastric cancer, the levels of the biomarkers are associated with cancer stage, metastasis, recurrence and resistance to treatment. The inconsistent outcomes from several studies on miRNAs note the necessity for more tests on this biomarker[133,134].

Other cancers potentially related to H. pylori

H. pylori infection is linked to MALT lymphoma[109-111]. Nearly 98% of MALT lymphomas are *H. pylori* dependent because prolonged infection with the pathogen leads to proliferation of the lymphoid tissue. Eradication of *H. pylori* infection used as a cure for *H. pylori*-positive MALT lymphoma was found to correlate with the remission in 60%-80% of MALT-lymphoma cases[111,140]. The presence of *H. pylori* in the host elevates the risk of developing other lymphomas, such as diffuse large B cell lymphoma and ocular adnexal lymphoma[3]. Contradictory results leave unclear the influence of the pathogen and of eradication therapy on carcinogenesis. Several studies have shown that *H. pylori* infection is correlated with laryngeal squamous cell carcinoma[140-142]. CagA-positive strains were found to cause a more severe condition and reduce the survival rate. However, not all cases confirm such an association[3]. Colorectal cancer development is also considered to be related to *H. pylori* infection[143-146]. High rates of mortality in specific regions from colorectal and stomach cancer, as well as high prevalence of the pathogen in critical colorectal adenomas point to *H. pylori* as a mutual risk factor. Some studies are in opposition to this theory because the pathomechanisms are not fully understood. An association between *H. pylori* infection and hepatocellular carcinoma has been suggested[147,148]. Esmat *et al*[149] have suggested that the presence of CagA positive *H. pylori* strains in the liver may cause progression of hepatocellular carcinoma due to infection with hepatitis C virus (HCV). The link between *H. pylori* infection and hepatic carcinoma has been confirmed by detection of genetic material of these bacteria in hepatic tissue[150]. The possibility of corelation between *H. pylori* infections and the development of pancreatic cancer has been suggested[151]. The role of gastric carriage of *H. pylori* $CagA^+$ strains, in increasing a risk for gastric ulcer as well as gastric and pancreatic cancers was shown on the basis of seroprevalence of *H. pylori* by Stolzenberg-Solomon

et al[152]. Meta-analysis performed by Trikudanathan *et al*[153], suggested a reduced statistically significant association. In addition, other data support the hypothesis of a correlation between pancreatic cancer and *H. pylori* as well as the ABO genotype due to its role in gastric secretion and the secretory activity of the pancreas[154-156].

H. PYLORI DIVERSITY *VS* GASTRIC CANCER RISK

CagA variation

The course of *H. pylori* infection depends on complex interactions between the microbial agent and the host genetic background, as well as host immune profile. *H. pylori* is a diverse microorganism. Specific features of an individual strain can determine the severity of inflammation and its consequences, including the promotion of malignancy. This diversity refers to the most important virulence factors, such as CagA, VacA toxin and OMPs.

CagA induces *in vitro*, the 'hummingbird' phenotype of epithelial cells of the stomach with symptoms of cell elongation. These cellular changes are similar to epithelial-mesenchymal transition (EMT), which occurs during development of gastric cancer stem cells (CSC). *H. pylori* CagA promotes EMT phenotype, which was studied on the basis of both mesenchymal markers and CD 44 molecules associated with CSC[157]. The presence of CagA with phosphorylated Glu-Pro-Ile-Ala-Tyr, called the EPIYA motif, in host cells induces changes in the cytoskeleton, modifications of intercellular connections and deregulation of the expression of genes encoding transcription factors. EPIYA motifs in the C terminal region of CagA determine its interaction with numerous host proteins. Multimeric, non-phosphorylated CagA protein enhances the activity of phosphorylated CagA protein and contributes to the loss of cell polarity[11,28]. Within the EPIYA motif there is a phosphate acceptor tyrosine domain. This region is polymorphic since it contains different numbers of EPIYA motifs. Moreover, the diversity was also found in regions among EPIYA sequences. The length polymorphism at the 3' end of the *cagA* gene results with increased phosphorylation of CagA protein, which enhance its biological activity and promotes more severe disease outcome[158]. Four EPIYA motifs have been described: -A, -B, -C, and -D. Their combination depends of geographic regions[159]. In general Western *H. pylori* strains possess EPIYA -A, -B, and -C whereas strains from East Asian region EPIYA -A, -B, and -D. The East Asian CagA-positive *H. pylori* strains are more closely associated with gastric cancer[160].

Vaziri *et al*[161] studied the influence of EPIYA motifs on the transcriptions of genes related to gastric cancer by using transfected gastric cancer AGS cell line with a eucaryotic vector carrying the *cagA* gene: ABC and ABCCC types. They found that the CagA oncoprotein of ABCCC type can induce intestinal metaplasia, IL-8 production by epithelial cells, dysfunction of Crk adaptor proteins, and anti-apoptotic and carcinogenic effects more intensively than the CagA protein of the ABC type.

The association between the number of EPIYA-C regions and increased CagA tyrosine phosphorylation, protein tyrosine phosphatase (SHP)-2 binding activity, cytoskeletal alterations, IL-8 expression in gastric mucosa, development of the hummingbird cell phenotype and severe disease frequency was found[162].

Western and East Asian CagA proteins differ in sequence among the EPIYA motifs. The FPLKRHD-KVDDLSKV sequence, which is present in Western type CagA in East-Asian type CagA is substituted by KIASAGKGVGGFSGA sequence. This amino acid sequence variation is supposed to be responsible for the higher frequency of gastric cancer in Japan as compared to the Western coutries[162]. Jones *et al*[159] verified that the East Asian EPIYA phenotype is closely related with disease development. Phosphorylated CagA regions are primarily EPIYA-C and -D sites, which are required for binding to SHP-2 and its activation[159].

Chattopadhyay *et al*[158] have suggested that in India, the infections related to different structures of CagA can be multiple. In this case the disease course is not determined by a particular type of CagA. They concluded that the risk of developing the disease is also associated with polymorphism of genes encoding other *H. pylori* proteins, as well as with the host genotype[158].

Research on a group of 436 Brazilian patients by Batista *et al*[163] showed that *H. pylori* strains in this region are the Western type and that there is a tight correlation between the number of EPIYA-C segments and increased risk of gastric carcinoma but not duodenal ulcers[163] similarly as in Caucasian population from Italy and American patients in Texas[164,165].

Regardless of the C/D type, most CagA molecules include single A- and B- tyrosine phosphorylation motifs (TPMs) that do not undergo simultaneous tyrosine phosphorylation[166]. Phosphorylated A- or B-TPMs have host interaction partners distinct from C- or D-TPMs and from each other, suggesting unique signaling functions. Zhang *et al*[166] showed that in the Western population, also, the polymorphism of the EPIYA-B motifs influences the frequency of disease development, suggesting that a single nucleotide polymorphism in a major bacterial interactive compound could promote a disease outcome. In this study, the CagA B-TPM sequences showed the highest variability. The EPIYA motif was present in 72.6% of B-TPMs. However, other EPIYA-like motifs have been identified (EPIYT, ESIYT, ESIYA, GSIYD). The analysis carried out by Zhang *et al*[166] demonstrated that the association of EPIYT segments with gastric cancer is lower than the EPIYA motifs.

The correlation, which was found between EPIYA

motifs and the level of IL-8 as well as a strength of inflammatory response in gastic mucosa may depend on the geographical region[167]. Fajardo *et al*[162] and Reyes-Leon *et al*[167] did not show correlation between the number of EPIYA-C motifs and IL-8 induction in the Columbian as well as Mexican population whereas Argent *et al*[168] obtained an opposite results for English population. Interestingly, Mexican and Columbian *H. pylori* strains share common predominant polymorphisms (ABC and ABCC). Hatakeyama has suggested that CagA is involved in gastric carcinogenic processes through a hit-and-run mechanism, in which pro-oncogenic activities of CagA are successively taken over by a series of genetic and/or epigenetic alterations compiled in cancer-predisposing cells during long-lasting infection with *cagA*$^+$ *H. pylori*[29].

VacA variants

VacA is a polymorphic toxin with pore forming activity and there are different allels of *vacA* gene within *H. pylori* strains. VacA is composed of four regions, which are further subdivided. The signal (s) region, which includes the N-terminus and a signal sequence is classified as s1 or s2[169]. The s region influences the formation of anion channel[170]. The mid (m) region, which affects host cell tropism, is classified as m1 or m2[169,170]. The intermediate (i) region is classified as i1, i2, or i3[169]. This region determines the vacuolating and cancerogenic activity of VacA toxin[171]. The d region means the deletion of 81 bp between the i- and m-regions. Without deletion it is classified as d1 or d2 if a 69 to 89 base pair deletion is present[169,171]. VacA virulence depends on the combination of individual parts. The *vacA* s1/m1 alleles determine high cytotoxic activity of VacA. By comparison the s1/m2 and s2/m2 genotypes are not cytotoxic. The s1/m1 profile is strongly correlated with the outcome of duodenal ulcers, peptic ulcer disease, progression of preneoplastic lesions, and gastric cancer[169,170]. Ogiwara *et al*[172] showed that the risk of gastric cancer in Western countries is related to the s1, m1, i1, and d1 polymorphisms, which are potentially linked with an increased neutrophil infiltration and gastric mucosal atrophy[171]. However, in other studies such a correlation was not found in East Asian countries[171,172].

It was found that i1 variants of the VacA protein have stronger vacuolating activity than i2 variants. Moreover, the i1 region is considered a better predictor of disease severity than the s1 and m1 variants in Western strains. The i region may contain A, B, and C polymorphic domains. The VacA toxicity depends on B and C part[170].

OMPs

Genes encoding OMPs consist 4% of *H. pylori* genome. Many *H. pylori* OMPs belong to OMP family 1, which contains various *H. pylori* outer membrane proteins (Hop) and Hop-related proteins (Hor). *H. pylori* OMPs are crucial for adaptation of the pathogen to the host. They play a role in bacterial movement and adhesion to gastric tissue[7]. Adhesins with known binding specificity include BabA (HopS), which binds Lewis^b, a fucosylated blood-group antigen that is present in gastric tissue[31] and SabA (HopP), which is a sialic acid-binding adhesin associated with higher colonization density in humans[173]. The *alpAB* locus has been shown to encode the outer membrane adhesins AlpA and AlpB, which bind laminin[174]. The HorB protein is another adhesin, however, its ligand has not been identified[175].

The best-characterized OMP of *H. pylori* is BabA, which is encoded by the *babA2* gene[176]. Research carried out by Torres *et al*[176] on a group of 130 *H. pylori* isolates from dyspeptic Cuban patients showed that the presence of a 'triple positive' genotype (*vacAs1*, *cagA* and *babA2*) (56.2% isolates) is correlated with the appearance of peptic ulcers, intestinal metaplasia and gastric cancer. Infection with these strains was found to be associated with a higher degree of inflammation and gastroduodenal lesions[176].

Research on 167 *H. pylori*-positive patients conducted by Zambon *et al*[177] allowed patients to be divided to four groups (A, B, C and D) on the basis of bacterial genotypes: *cagA*(-), *s2 m2*, *babA2*(-); *cagA*(+), *s1 m1*, *babA2*(+); *cagA*(+), *s1 m2*, *babA2*(+); *cagA*(+), *s1 m2*, *babA2*(-), respectively, that differ in their ability to induce gastrointestinal diseases. *H. pylori* strains of group B induced the worst inflammatory response including intestinal metaplasia[177]. Moreover, a relationship between *cagA* and the *s1* and *m1* alleles of *vacA* and *oipA* was found. By comparison, *H. pylori* strains without *cagA* were usually *babA2*(-) and *oipA*(-) and they held the *s2* and *m2* *vacA* alleles. This observation confirmed the role of the pathogenicity island as the main vehicle of virulence genes[177].

Another important Hop is HopH, encoded by the *HP0638/hopH* gene[178]. The *hopH* genotype has been foud related to *H. pylori* virulence markers including *vacAs1, vacAm1, babA2,* with the strongest association to *cagA.* The association of the *hopH* gene with gastric disorders could be due to promotion of increased bacterial adherence and colonization by the hopH. The expression of *hopH* has been found regulated by phase variation within a CT dinucleotide repeat motif[178].

Host genetic susceptibility and immune profile

The long lasting inflammation induced by *H. pylori* infection is followed by DNA damage, the impairement of repair processes and increased rate of mutations. These phenomena promote the development of *H. pylori*-related gastric carcinogenesis[128-132,179].

Pattern recognition receptors

Pathogens possess many conservative PAMPs. These structures, which are present in various groups of

microorganisms, have not changed during evolution and do not occur in human organisms.These compounds are recognized by PRRs, which are deposited on immune cells as well as epithelial cells and vascular endothelium. TLRs and damage-associated molecular patterns (DAMPs) are representative PRRs[180,181].

Various groups of receptors are simultaneously engaged in recognition of *H. pylori* compounds and the development of gastric cancer. These are TLR2, TLR3, TLR4, TLR5, and TLR9; nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), such as NOD1, NOD2, and NLRP3 (NLR family pyrin domain containing 3); dendritic cell-specific intercellular grabbing non-integrin; retinoic acid-inducible gene (RIG)-I-like receptors (RIG-I); and melanoma differentiation associated protein 5. Polymorphisms in genes, which are involved in the signaling cascades *via* TLR, NLR, apoptosis-associated speck-like protein, and caspase recruitment domain containing protein 8 (CARD8) can increase the risk of *H. pylori* infection and gastric cancer[182,183]. This can happen because the dysfunction of genes, which are involved in cell signaling pathways *via* the above receptors may significantly modulate the host immune response during *H. pylori* infection[183].

TLR4

TLRs recognize various *H. pylori* PAMPs, including flagellin (TLR5) and unmethylated CpG motifs (TLR9) as well as LPS (TLR4/TLR2)[183].

The expression of TLR2, TLR4 and TLR5 increases during gastric dysplasia and especially a strong correlation between TLR4 and gastric carcinoma has been suggested[184]. Additionally, Chochi *et al*[185] found that binding of *H. pylori* LPS to TLR4 resulted in increased growth of gastric adenocarcinoma. On this way also antitumor activity of human mononuclear cells was diminished.

In recent studies, much attention has been paid to the influence of TLR receptor polymorphisms on the development of diseases associated with *H. pylori* infection. Single nucleotide polymorphisms (SNPs) of the TLR4 receptor were connected with an increased risk of gastric carcinoma, including *TLR4* rs4986790 (Asp299Gly)[186,187], *TLR4* rs4986791 (Thr399Ile)[187], *TLR4* rs10116253, *TLR4* rs10983755, *TLR4* rs11536889 (C3725G/C)[182], *TLR4* rs1927911[183]. *TLR4* Asp299Gly and Thr399Ile polymorphisms located in the encoding region have been considered the most important since they diminish the stability of the TLR4 extracellular domain[182,187].

Another study conducted by Bagheri *et al*[186] on a group of 195 patients with *H. pylori* infection and 241 *H. pylori* not-infected individuals confirmed that the increased frequency of *TLR4* (Asp299Gly) G and DG alleles was related to chronic active gastritis. An A-G substitution at 896 bp was associated with a decreased response to LPS *in vivo* and *in vitro* and an increased risk of inflammatory disease. The results obtained by Castaño-Rodríguez *et al*[182] confirmed that in the Western population the *TLR4* Asp299Gly G allele as well as the *TLR4* rs11536889 C allele and the CC genotype increased the risk of gastric cancer or other inflammation-related cancers. These results indicate that there is a relationship between the *TLR4* rs11536889 polymorphism and increased incidence of cancer, which is consistent with the fact that the *TLR4* rs11536889 polymorphism is located in the center of the 2818-bp *TLR4* 3'UTR and, therefore, may affect mRNA stability. However, other studies of polymorphism investigated in Asian and Caucasian individuals have shown different risk associations with gastric cancer in an ethnic-specific manner[182].

TLR2

In *H. pylori* infection, much attention is also focused on TLR2. It has been shown[188] that *H. pylori* LPS as TLR2 ligand induces the secretion of chemokines by gastric epithelial cells due to acting on tribbles 3 (TRIB3) protein, which is involved in the expression of the nuclear factor NF-κB. However, both TLR4 and TLR2 are engaged in the response of host immune cells against *H. pylori*, which effectiveness depends on the polymorphism of those receptors[183]. Meta-analysis of *TLR2* -196 to -174 deletion and risk of gastric cancer conducted on 1364 gastric cancer patients and 2487 controls showed that there is an association between this polymorphism and risk of gastric cancer in the Japanese population. Polymorphism at this position decreases the induction of IL-8 secretion, thus impairing the response to *H. pylori*. Interestingly that correlation failed to be shown in the Chinese population, which may indicate an ethnic consideration in the incidence of stomach cancer[182].

CD14

CD14 molecule and TLR4 both participate in the recognition of LPS[189]. During *H. pylori* infection monocytes and macrophages have been shown to release IL-12 in response to CD14 - dependent activation. This was correlated with the infiltration of gastric mucosa with T helper 1 lymphocytes and the maintenance of chronic inflammatory response[190].

Two SNPs identified in the promoter region of the *CD14* gene: -260C/T (rs2569190 or *CD14* -159) and -561C/T (rs5744455), have been suggested to increase the susceptibility to gastric cancer[182,191]. The *CD14* -260 T allele had decreased affinity for the binding with DNA of transcription factors such as stimulatory proteins (SP) 1, SP2 and SP3 of which SP3 downregulates the activation of the cells by SP1 and SP2. Thus, the SP3 to SP1 and SP2 ratio might play an important role in the regulation of CD14 transcription[182,192,193]. Although an increased transcription activity of this allele has been demonstrated in monocytes with low levels of SP3 a direct correlation between

CD14 polymorphism and gastric cancer incidence still needs to be investigated[190].

NODs

The NOD-like receptors detect PAMPs localized intracellularly as well as cellular DAMPs released due to elevated stress conditions. These receptors are involved in the development of innate immunity, regulation of inflammatory response and programmed cell death. Among NODs the binding specificity of NOD1 and NOD2 is different. NOD1 binds γ-D-glutamyl-meso-diaminopimelic acid whereas NOD2 muramyl dipeptide[194,195].

During *H. pylori* infection NOD1 is engaged in the induction of NF-κB and activator protein 1 (AP-1), which are involved in cytokine synthesis and cell activation, thus triggering inflammatory response[190,196-198]. It has been shown that NOD1 regulates direct killing of *H. pylori* by antimicrobial peptides[199], enhances IFN-γ signaling in gastric epithelial cells during *H. pylori* infection, particularly with *cag*-PAI positive strains and exacerbates disease severity[198,200]. NOD2 induces pro-IL-1β and is necessary for the induction of NLRP containing protein 3 (scaffolidng proteins of inflammasomes) in *H. pylori*-infected dendritic cells[201].

Polymorphism among NOD receptors also has an impact on the rate of stomach cancer incidence. Wang *et al*[202], carried out a test on a group of 296 patients with gastric cancer and 160 healthy subjects in the Chinese population, which showed that the *NOD1* rs2907749 TT polymorphism reduced the likelihood of cancer of the stomach but *NOD1* rs7789045 TT increased the incidence of stomach cancer (especially in the case of the *NOD2* genotype rs7205423). An enhanced NOD1 expression was detected in *H. pylori* infected gastric mucosa. This might suggest that signaling *via* NOD1 determines gastric inflammation[202]. In general there is no association between *NOD1*/*NOD2* mutations and gastritis as well as gastric ulcer. However, association between the R702W mutation in the *NPD 2/CARD15* gene and gastric lymphoma has been found. The risk of gastric lymphoma is higher in those who carry allele T as compared to control individuals[200]. Companioni *et al*[203] have found a significant association between SNPs in *CD14*, *NOD2* and *TLR4*. This study revealed that genetic variation in NOD2 associates with nocardia gastric cancer while variation in CD14 is associated with cardia gastric cancer.

INFLAMMATION DRIVEN MALIGNANCY RISK

Cytokines

During *H. pylori* infection the immune and gastric epithelial cells respond by the secretion of cytokines (pro- and anti-inflammatory). The level of cytokines might depend on polymorphisms of the genes encoding specific cytokines including tumor necrosis factor (TNF)-α, IL-1, IL-8 and Il-10[204]. Genetic polymorphisms have been considered as factors increasing cytokine levels and susceptibility for cancer development due to hypochloridria[205].

IL-1

IL-1 (IL-1α and IL-1β), is a pro-inflammatory cytokine and IL-1 receptor antagonist (IL-1Ra) possess a natural anti-inflammatory activity. The initiation or the maintenance of inflammation depend on the balance between IL-1β and IL-1Ra[204]. IL-1β and IL-1RN gene polymorphisms increase risk of hypochloridria and gastric carcinoma. This is because the elevated levels of IL-1 initiate spontaneous inflammation, which then can be followed by dysplasia and gastric carcinoma through an activation of the IL-1/NF-κB pathway[206-208]. It has been shown that IL-1β significantly amplifies inflammatory response during *H. pylori* infections[204,205]. Ramis *et al*[204], investigated in the *IL-1B* gene three SNPs (C-T transition at -31 position; C-T transitions at -511 and +3954 positions), associated with an enhanced secretion of IL-1β. In *H. pylori* infected patients there was a correlation between IL-1β level and the T/T genotype (-511 position) as well as the C/C genotype (-31 position). In such patients an increased risk of gastritis but not peptic ulcer and gastric carcinoma has been found. This research group also proved that patients with the T/T genotype of *IL-1B* (-511 position) were more frequently infected with *H. pylori cagA*(+) strains. There was no correlation between *IL-1B* gene polymorphisms at position +3954 and increased prevalence of *H. pylori* infection as well as *H. pylori*-derived diseases[204].

However, in the Costa Rican population two proinflammatory genotypes *IL-1B*+3954 T/C and *IL-1RN**2/L were foud related to gastric cancer cases[209]. Caleman Neto *et al*[210], have suggested that the *IL-1B* -31T/T polymorphism acts as a protective factor against *H. pylori* infection in the Brazilian population.

Contrary to previous studies, Al-Moundhri *et al*[211], has proven that the widely reported association between *IL-1B* -31/-511 polymorphism and gastric cancer was not established in the Omani Arab population, supporting the ethnic differences in the effect of *IL-1B* polymorphism on gastric cancer development.

IL-1RN

Il-1RN as an antagonist of the IL-1 receptor modulates its activity. The most intensively studied *IL-1RN* polymorphism connected to gastric cancer outcome is a 86-bp variable number of tandem repeats polymorphism in the *IL-1RN* second intron (*IL-1RN**2)[208]. The study carried out on the Brazilian Amazon population by Melo Barbosa *et al*[205], showed that among patients with gastric ulcer and adenocarcinoma there was a higher frequency of allele 2 carriers (*IL-1RN*2*).

The IL-1Ra protein (encoded by the *IL-1RN* gene) competes with the IL-1 receptor to inhibit the action induced by IL-1β. The presence of the *IL-1RN*2* variant is connected with the increased levels of IL-1β in the gastric mucosa and to hypochlorhidria in comparison to *IL-1RN1/1* variant[205]. Research performed on a group of 118 gastric cancer patients and 245 healthy controls also supported the correlation between the presence of the *IL-RN*2* allele and the increase in the gastric cancer ratio in the Arab population[211].

Tumor necrosis factor alpha

TNF-α is a cell signaling protein involved in systemic inflammation and acute phase reaction. This cytokine is produced by activated macrophages, CD4+ lymphocytes, NK cells, neutrophils, mast cells, eosinophils, and neurons. It takes part in the regulation of immune cell activity, fever induction, apoptotic cell death, cachexia, inflammation, inhibition of tumorigenesis and viral replication. It is also involved in the cytokine response during sepsis[212,213]. The elevated secretion of TNF-α is observed in the gastric mucosa of *H. pylori* infected patients where this cytokine induces cell apoptosis[214]. The activity of TNF-α is regulated by soluble TNF receptors (sTNF-Rs), which potentially protect gastric epithelial cells colonized by *H. pylori* from apoptosis[214].

TNF-α activity and concentration can be influenced by SNPs (G to A transitions at -308A and -238 positions) in the promoter region of *TNF-α* gene[215]. In the Korean population the transition at -308 position was related with a CagA(+) *H. pylori* infections and its severe consequences. The biallelic polymorphism at this position is associated with the development of gastric carcinoma in the Caucasian population[205].

The binding of AP-2 to -308 region was found by Yea *et al*[215] to be altered by the −308A allele. Due to this -308A polymorphism might lead to an increase in *TNF-α* gene expression[215].

The latest results of meta-analysis obtained by Sun *et al*[216] demonstrate that *TNF-α* -308G/A and -1031 T/C polymorphisms may be protective factors against *H. pylori* infection, whereas -863C/A substitution may be a risk factor, especially in Asian populations. The authors also showed that there was no significant association between -857C/T polymorphism and *H. pylori* infection while -863C/A significantly increased the risk of infection. Moreover, the -1031T/C polymorphism decreased this risk for the Asian subgroup and hospitalized patients[216].

IL-10

IL-10 is a pleiotropic cytokine, which has the ability to suppress or stimulate anti-cancer properties of immune cells. This cytokine downregulates the production of pro-inflammatory cytokines by inhibition of Th 1 lymphocytes and stimulation of B, as well as Th 2, lymphocytes and thus downregulates the inflammatory response[212,213]. Since 2003 researchers have consistently reported associations between *IL-10-592* A/C SNP and susceptibility to gastric cancer but with mixed or conflicting results[217]. A meta-analysis performed by Ni *et al*[218] indicated that in Asian populations the carriers of *IL-10* -1082 GG-plus-GA genotypes are more susceptible to all types of gastric cancer.

Kim *et al*[219] investigated three *IL-10* promoter polymorphisms: -1082A/G, -819T/C, and -592 A/C probably related to elevated levels of IL-10. These polymorphisms were associated with an increased risk of intestinal-type noncardiac gastric cancer but only in *H. pylori* infected smokers[219].

Con *et al*[209] showed that the *IL-10* -592 A/A or -592 C/A polymorphisms were associated with an increased risk of gastric cancer in the Costa Rican population. In the above study the *IL-1β* +3954 T/C, *IL-1RN**2/L and *IL-10*: -592 C/A polymorphisms, in the patients infected with *H. pylori vacA s1b/m1* strains have been found to predispose them to gastric cancer. It means that synergistic effect of bacterial and host genotypes may influence the course and the consequences of *H. pylori* infection[209].

IL-8

During early phase of *H. pylori* infection a chemotactic IL-8 induces infiltration of granulocytes to the site of infection and induction of phagocytosis once they have arrived[204]. Activation of phagocytes in the inflammatory milieu may result in gastric barrier damage due to releasing of proteolytic enzymes and reactive oxygen radicals[220].

As in the case of other cytokine polymorphisms, IL-8 differentiation is also the subject of research. Caleman Neto *et al*[210] suggested that in Eastern populations the elevated production of IL-8 and the intensity of the inflammatory response depends on the presence of the A allele in the promoter region of the *IL-8 gene* (-251 position).

Ohyauchi *et al*[220] investigated a correlation between *IL-8* polymorphism and gastroduodenal disease outcome during *H. pylori* infection in the Japanese population. Thy showed that in *H. pylori* infected patients the presence of *IL-8* -251A allele was linked with the gastric ulcer, gastric atrophy and then cancer. This study confirmed that, in comparison to the *IL-8* -251T variant, *IL-8* -251A transcription is activated in more active gastritis with strong neutrophil infiltration. These results have been confirmed by the study of Caleman Neto *et al*[210], performed with 60 patients, which showed that the *IL-8* -251TT genotype could protect whereas the *IL-8* -251TA genotype could promote the *H. pylori* infection.

Cyclooxygenase-2

Cyclooxygenase-2 (COX-2) catalyzes the conversion of arachidonic acid to prostaglandins and its

production increases in response to growth factors, cytokines and mitogens. COX-2 is often undetectable in normal tissues, whereas in tumor tissue specimens its expression is higher[221,222]. Specifically, increased COX-2 expression is linked to the progression of gastric cancer and precancerous tissues by activating angiogenesis, inhibiting apoptosis, and accelerating invasion and metastasis[221]. In addition to cytokine polymorphisms, genetic differentiation of cyclooxygenase also plays an important role in the development of *H. pylori*-associated gastric diseases[222]. Concerning the polymorphisms of promoter region of *COX-2* (1195G/A and -765G/C), Li *et al*[222] showed that the increased risk of gastric cancer appears in the carriers of the *COX-2*-1195AA but not of the *COX-2*-765G/C genotype.

Meta-analysis carried out by Zhao *et al*[221] showed that the -765G/C polymorphism (rs20417) in the promoter region of the *COX-2* gene could be a risk factor for gastric cancer in Asians and Indians. This SNP affects the transcription and functional activity of COX-2. The *COX-2*-765G/C polymorphism was significantly associated with an increased risk of gastric cancer, regardless of *H. pylori* infection.

Polymorphisms involved in deregulation of T cell response

Gastric MALT lymphoma depends on the activation of specific T lymphocytes, which undergo regulation through different mechanisms. It depends on cytotoxic T-lymphocyte antigen (CTLA) 4 as well as CD28 and inducible costimulator (ICOS) genes[223-225]. Genotyping of *CTLA 4* gene (49 A/G, -318 C/T, CT60 A/G), *CD28* gene (IVS3+ 17T/C), and *ICOS* gene (c.602 A/C and c.1624C/T) has been performed by Cheng *et al*[226] in the gastric MALT lymphoma patients with or without *H. pylori* infection and healthy individuals. The *CTLA 4* -318 C/T genotype was associated with a lower whereas the *CTLA 4* 49 G/G genotype with a higher risk of MALT lymphoma. In *H. pylori*-positive patients, the susceptibility to MALT lymphoma was four times higher in the case of the carriage of -318C -49G haplotype.

CONCLUSION

H. pylori has evolved during long cohabitation with humans. The colonization of the host stomach at a young age, persistence in this specific niche for its lifetime, subversion of the human immune system by hypoinflammatory LPS and molecular mimicry, and induction of gastritis and cancer development make *H. pylori* a complex pathogen. The clinical aspects of *H. pylori* depend on several conditions, such as the location of infection, the host susceptibility, the bacterial strain and environmental factors. The virulence strategies of bacterial CagA-positive strains, as well as low socioeconomic status of the patient, influence the outcome of the infection. The highest prevalence rates of infection are reported in Asia and Africa. For years *H. pylori* infection might remain asymptomatic in spite of the developing condition. Medication for chronic gastritis or peptic ulcers involves antibiotic therapy. Sequential therapy is the most efficient treatment to cure the infection. To prevent the occurrence of antibiotic resistance, only cases with clinical symptoms or asymptomatic patients in a risk group ought to be treated. Adequate results for *H. pylori* detection are provided by the non-invasive urea breath test and invasive nested PCR. Eradication of the infection typically leads to improved patient health, but it may allow the development of gastroesophageal disease and asthma. The intensity of the infection reflects the ability of *H. pylori* to induce extragastric diseases. Chronic atrophic gastritis is the precursor condition for ulceration and gastric malignancy. Classified as a group I carcinogen and causing nearly 670 thousand new cancer cases every year, *H. pylori* has become a threat to our lives. Specific biomarkers are crucial for early diagnosis of gastric cancer. Although *H. pylori* is one of the most studied pathogens of the upper gastrointestinal tract, many of its mechanisms of action are still not well understood.

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P- Reviewer: Cover TL, Vaziri F **S- Editor**: Gong ZM
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ISSN 1007-9327
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