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Molecular Mechanisms of *Helicobacter pylori* Pathogenesis

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Helicobacter pylori infects 50% of mankind. The vast majority of *H. pylori* infection occurs in the developing countries where up to 80% of the middle-aged adults may be infected. Bacterial infection causes an inflammatory response that proceeds through a series of intermediated stages of precancerous lesions (gastritis, atrophy, intestinal metaplasia, and dysplasia). Among infected individuals, approximately 10% develops severe gastric lesions such as peptic ulcer disease, 1–3% progresses to gastric cancer (GC) with a low 5-year survival rate, and 0.1% develops mucosa-associated lymphoid tissue (MALT). GC is one of the most common cancer and the third leading cause of cancer-related deaths worldwide. In this review, we have summarized the most recent papers about molecular mechanisms of *H. pylori* pathogenesis. The main important steps of *H. pylori* infection such as adhesion, entry in epithelial gastric cells, activation of intracellular pathways until epigenetic modifications have been described.

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Helicobacter pylori is considered the most common etiologic agent worldwide in adults and children. It infects 50% of mankind (Parreira et al., 2013) and represents the most important risk factor for gastric malignancies (Wang et al., 2014). For this reason, the International Agency for Research on Cancer (IARC) has classified it as a class I carcinogen (IARC, 1994). The prevalence of *H. pylori* varies with the geographic regions, age, socio-economic status, educational level, living environment, and occupation (Wang et al., 2014). The vast majority of *H. pylori* infection occurs in the developing countries where up to 80% of the middle-aged adults may be infected (Wang and Peura, 2011; Wang et al., 2014). Natural acquisition of *H. pylori* infection occurs, for the most part, in childhood via fecal–oral and oral–oral pathways (Alvarez et al., 2013a; Sampieri, 2013). Infection induces an inflammatory response that does not eradicate the bacterial colonization, but which persists for the lifetime of the individual (Logan and Walker, 2001; Parreira et al., 2013). The slow sequence, known as Correa's cascade (Correa, 1992) passes through a series of intermediated stages of precancerous lesions in the following order: gastritis, atrophy, intestinal metaplasia, and eventually dysplasia (Boreiri et al., 2013). Among infected individuals, approximately 10% develops severe gastric lesions such as peptic ulcer disease, 1–3% progresses to gastric cancer (GC) with a low 5-year survival rate (Cirak et al., 2007), and 0.1% develops mucosa-associated lymphoid tissue (MALT) lymphoma (Noto and Peek, 2012; Parreira et al., 2013; Wang et al., 2014) (Fig. 1). It is estimated that individuals infected with *H. pylori* have more than twofold increased risk of developing GC compared with non-infected ones (Queiroz et al., 2012; Demirel et al., 2013). Although a dramatic decline in the incidence and mortality has been observed in recent decades, GC is one of the most common cancer and the third leading cause of cancer-related deaths worldwide with more than 700,000 deaths annually (Melton et al., 2010; Boreiri et al., 2013; Shiotani et al., 2013). GC is an insidious disease, often manifesting its symptoms at an advanced stage when few therapeutic options are available with even less efficiency (Boreiri et al., 2013). GC arises from hyperproliferation of the stomach epithelial cells and are accompanied by hypochlorhydria (low-acid secretion), and atrophic gastritis (Fox et al., 2006; Osman et al., 2013).

H. pylori gastritis is characterized by infiltration of the gastric mucosa with both acute inflammatory cells (polymorphonuclear leukocytes) and chronic inflammatory cells (lymphocytes, plasma cells, and macrophages). *H. pylori* initially are predominantly localized at the antrum, a site where parietal (acid producing) cells are absent and thus acid secretion is not directly affected (Shiotani et al., 2013). The progression and severity of the gastritis pattern depend on an interaction of multiple factors:

(1) *H. pylori* features including genomic plasticity, capacity for adaptation to the individual host conditions, modulation of the reaction to the host immune system response and presence and production of various virulence factors;

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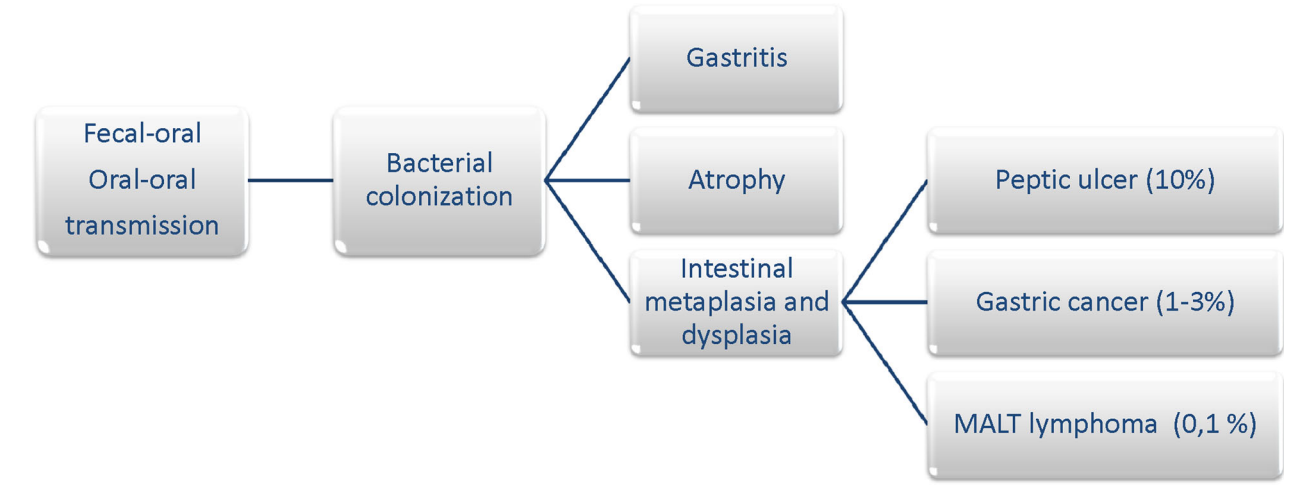

Fig. 1. Sequence of subsequent events from bacterial transmission to the host until precancerous and gastric lesions induced by *H. pylori*.

(2) host factors, for example, genetic background or physiological and immunological state, especially those that enhance or reduce the inflammatory response to the infection;
(3) the environmental factors such as smoking, diet, high salt, and meat consumption (Hnatyszyn et al., 2013; Sampieri, 2013; Shiotani et al., 2013).

Only a subset of infected individuals develops serious gastric disease and the mechanism of *H. pylori* pathogenicity is not well understood (Lillehoj et al., 2012; Chiariotti et al., 2013). The mechanism by which *H. pylori* causes disease in humans can be described as a multi-step process where the bacterium first has to evade the bactericidal activity of the gastric acid barrier and enter the mucous layer (colonization) and then it has to adapt and multiply under the environmental conditions of the gastric mucus (persistence) (De Luca et al., 2004; Manente et al., 2008). Several bacterial virulence factors have been associated with the development of gastric diseases. The first step, essential in successful infection, is the adhesion of *H. pylori* to the host gastric mucosa and bacterial motility. This event triggers the expression of several bacterial genes, including some that encode virulence factors, and protects the pathogen from clearance mechanisms such as liquid flow, peristaltic movements, or shedding of the mucous layer (Kim et al., 2004; Parreira et al., 2013). Adhesion is mediated by *H. pylori* surface-bound proteins, termed adhesins, that recognize glycan structures (Gly-Rs) expressed on the surface of gastric epithelial cells and are also present on the mucus layer lining the gastric mucosa (Ilver et al., 1998; Mahdavi et al., 2002; Goncalves et al., 2013; Parreira et al., 2013). The blood group antigen binding adhesin (BabA) recognizes fucosylated blood group antigens, including the difucosylated Lewis antigens, such as the Lewis b (Le^b) antigen and H type 1 histo-blood group carbohydrate structures expressed in the gastric epithelium and mucus layer (Goncalves et al., 2013; Parreira et al., 2013). Infection with *H. pylori* strains expressing functional BabA have been correlated with an increased risk of gastric carcinoma (Ilver et al., 1998; Gerhard et al., 1999; Yamaoka et al., 2002; Parreira et al., 2013). The sialic acid-binding adhesin (SabA) mediates bacterial adherence to gastric mucosa through the bound with sialylated carbohydrate structures such as sialyl Lewis x and sialyl Lewis a (Mahdavi et al., 2002; Aspholm et al., 2006; Goncalves et al., 2013). Urease and flagellin have been recognized as important factors for bacterial colonization of the gastric mucosa (Dunn and Phadnis, 1998; O'Toole et al., 2000; Perrais et al., 2014). Urease is able to convert urea into ammonia and carbon dioxide in order to form an acid-neutralizing cloud of ammonia, elevating the pH to neutral, and protect the bacterium from gastric acidity (Celli et al., 2009; Perrais et al., 2014). Urea hydrolysis is accomplished by uptake of urea through a proton-gated channel that allows hydrolysis inside the bacterium and creating a thin neutral layer around the outer surface of the cell (Weeks et al., 2000; Celli et al., 2009). Moreover, it has been shown that urease can exist also on the cell surface (Phadnis et al., 1996; Dunn and Phadnis, 1998; Baik et al., 2004; Celli et al., 2009), or in the stomach environment (Vanet and Labigne, 1998; Gobert et al., 2002; Celli et al., 2009). Once the bacterium has created a favorable environment in term of pH, the next step is the ability to swim through the protective layer of the gastric mucus in the host stomach (Celli et al., 2009). It has been demonstrated that urease induced pH elevation of *H. pylori* reduces viscoelasticity in the mucin gel, triggering the transition from gel to sol of gastric mucin and enables the bacteria to move freely through the mucus (Celli et al., 2009). Flagella (5–7 per cell) confer motility to the cells; they are made of polymers of two subunits, the major flagellin FlaA and the minor flagellin FlaB (Perrais et al., 2014). Other than these factors cited above, an other important protein, the *Helicobacter* D,D-peptidase A (HdpA) has been identified for its involvement in determining *H. pylori* shape (Bonis et al., 2010). It has been demonstrated that mutation of HdpA induces abnormal shape and reduces the ability of *H. pylori* to colonize the gastric mucosa (Bonis et al., 2010). Moreover, *H. pylori* produces a variety of virulence factors able to deregulate host intracellular signaling pathways. Among all the virulence factors, Cag A (cytotoxin-associated gene A) and its pathogenicity island (Cag PAI), VacA (vacuolating cytotoxin A), heat shock protein B (HspB) (Iaquinto et al., 2000; De Luca et al., 2008), and the duodenal ulcer promoting gene A (DupA) are considered the major pathogenic factors (Lee and Derakhsham, 2013; Wang et al., 2014) (Fig. 2).

Molecular Mechanism of *H. pylori* Pathogenesis

The *H. pylori* genome consists of 1.65 million bp and codes for about 1,500 proteins (Tomb et al., 1997; Alm and Trust, 1999;

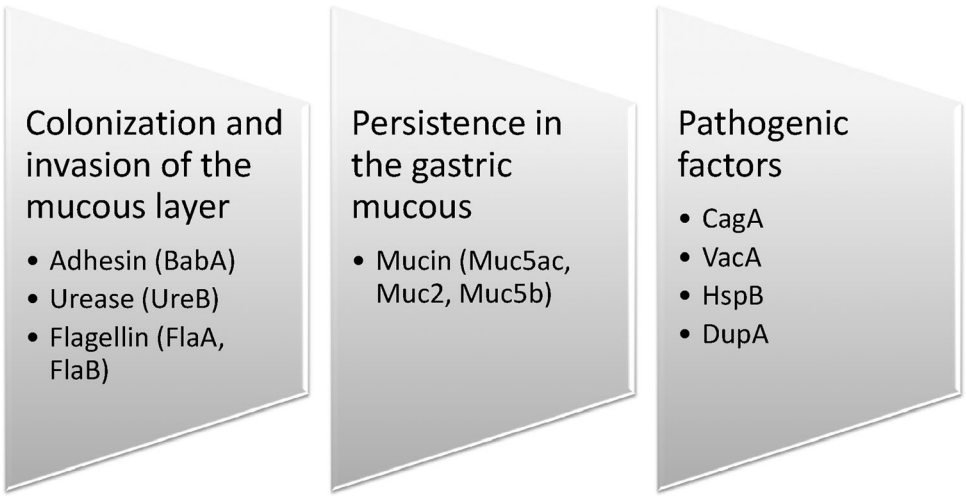

Fig. 2. Schematic representation of some bacterial factors involved in different stages of *H. pylori* pathogenicity.

De Luca et al., 2004). However, *H. pylori* populations are extremely different, as a result of point mutations, substitutions, insertions, and/or deletions in their genome (Blaser and Berg, 2001; Buommino et al., 2012).

Adhesion to gastric epithelium

The stomach is protected from its own gastric juice by a thick layer of mucus that covers the stomach lining (Penta et al., 2005). The mucus layer is formed by high molecular weight and heavily glycosylated glycoproteins known as mucins, whose function is to protect gastric epithelial cells against chemical, enzymatic, microbial, and mechanical damage. Mucins act as diffusion barrier to acidic HCl instilled into the lumen of the stomach and alkaline bicarbonate ions secreted by the gastric epithelium, maintaining a gradient from around pH 1.2–2.5 in the gastric lumen to pH ~7.4 near the epithelial surface (Bhaskar et al., 1992; Goncalves et al., 2013). *H. pylori* resides within the mucus of the stomach and duodenum and about 1% of the colonizing bacteria adheres to the apical surface of epithelial cells where they attach firmly via adhesin molecules and via modifications of cell membrane proteins and of cytoskeletal proteins (De Luca et al., 2004). This ecological niche requires special features to survive, but offers the advantage of little competition from other bacterial species (Montecucco et al., 1999; De Luca et al., 2004). MUC5AC mucin, the major component of the mucosal layer, is closely related to *H. pylori* and plays a role in the adhesion of this bacterium to the gastric mucosa (Van den Brink et al., 2000; Van de Bovenkamp et al., 2003; Shi et al., 2014). The expression level of MUC5AC is gradually decreased during the progression of types I, II, and III intestinal metaplasia and in the progression of *H. pylori* positive pre-neoplastic lesions to gastric adenocarcinoma (Machado et al., 2000; Shi et al., 2014). Particularly, the MUC5AC is lower in cancer tissues with more than five metastatic lymph nodes and positive to *H. pylori* as compared with that of the cancer tissues with five or less metastatic lymph nodes, which demonstrates that cancer progression might be related with the MUC5AC expression level (Shi et al., 2014). Recently, it has been reported that urease mediates downregulation of *MUC5AC* transcription in gastric cancer cells, since *MUC5AC* promoter contains UreB-responsive elements (Perrais et al., 2014). Moreover, UreB- and FlaA-responsive elements in the promoters of *MUC2*, *MUC5AC*, and *MUC5B* and CagA-responsive elements in the promoters of *MUC2* and *MUC5B* have been identified (Perrais et al., 2014). These results suggest that different bacterium virulence factors act during infection and development of gastric malignancies (Perrais et al., 2014). *H. pylori* is also able to inhibit the total mucin synthesis and causes significant alterations of the structure and function of gastric mucins (Fichman and Niv, 2004; Kocer et al., 2004; Marques et al., 2005; Kang et al., 2008; Lillehoj et al., 2012; Shi et al., 2014), which may be the key events in the progression to gastric cancer or malignant transformation (Nomura et al., 2004; Sun et al., 2005; Shi et al., 2014).

Activation of intracellular pathways of gastric epithelial cells

H. pylori strains can be divided into two broad families, type I and type II, based on the presence of the cag pathogenicity island (PAI), an approximately 40 kb locus composed of 31 genes (Censini et al., 1996; Tomb et al., 1997; De Luca et al., 2004) including the CagA protein and the Cag type IV secretion system (T4SS). The T4SS forms a needle-like structure protruding from the bacterial surface by which CagA can be inserted into the target host cells (Tegtmeyer et al., 2011; Ling et al., 2013; Wang et al., 2014). A member of T4SS is CagL that is able to target the T4SS to host $\alpha 5\beta 1$ integrin receptor on the epithelial cell membrane (Delahay and Rugge, 2012).

It has also been demonstrated that CagL interacts with $\alpha v\beta 3$ and $\alpha v\beta 5$ receptors responsible of the activation of the gastrin promoter (Wiedemann et al., 2012). CagL interacts with CagI (Shaffer et al., 2011; Pham et al., 2012) and CagH (Shaffer et al., 2011) forming a surface exposed T4SS subassembly required for pilus biogenesis (Delahay and Rugge, 2012). CagM is localized mainly in the bacterial membrane, partially in the periplasm. It is essential for CagA translocation and probably is one of the members of the transmembrane channel of T4SS (Ling et al., 2013). Once translocated in the host cytoplasm, CagA may bind to the inner surface of the cell membrane and undergoes tyrosine phosphorylation of its C-terminal A–B–C or D type glutamate–proline–isoleucine–tyrosine–alanine (EPIYA) motif by Src family kinases and c-Abl (Delahay and Rugge, 2012; Wang et al., 2014). The entry of CagA into the

cytoplasm through the ectodomain of α5β1 integrin, induces its interaction with a number of host proteins in order to activate downstream signal pathways, such as Ras/mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway (Mueller et al., 2012; Xu et al., 2012), nuclear factor κB (NF-κB) pathway, and β-catenin pathway (Wang et al., 2014). All these interactions between bacterial and host proteins allow the deregulation of epithelial cell polarity (cell elongation and scattering) and the acquisition of the so called "humming bird" phenotype (mediated by interaction with Src-homology protein tyrosine phosphatase (SHP) 2), disruption of tight junctions (impairing E-cadherin/β-catenin complex; inhibition of the kinase partitioning-defective 1b/microtubule affinity-regulating kinase 2-PAR1b/MARK2) and cell apical junction complex (interacting with several junction proteins such as *zonulaoccludens* 1, junctional adhesion molecule A). All these processes are able to facilitate the malignant transformation and development of intestinal metaplasia (Kaplan-Turkoz et al., 2012; Wang et al., 2014). CagA is also able to interact with the apoptosis-stimulating protein of p53 (ASPP2) that normally induces apoptosis following DNA damage by activating the tumor suppressor p53 (Delahay and Rugge, 2012). CagA misregulates ASSP2 leading to proteosomal degradation of p53 and consequently evokes an antiapoptotic response (Buti et al., 2011; Delahay and Rugge, 2012). In this view, it has been demonstrated that *H. pylori* $CagA^{+}$ strains significantly increase the risk of developing severe gastritis, atrophic gastritis, peptic ulcer, and distal gastric cancer (De Luca et al., 2004). Moreover, CagM and CagL components of T4SS mechanistically involve in NF-κB activation (Smolka and Backert, 2012) and in the repression of HKα transcription, which causes the downregulation of human gastric H/K-ATPase expression, significantly inhibiting acid secretion by gastric cells (Saha et al., 2010; Ling et al., 2013). On the other hand, VacA product might contribute to the pathogenicity of *H. pylori* inducing vacuolation of gastric cells, apoptotic events, and alteration in cell cycle (De Luca et al., 2004; Manente et al., 2008; Buommino et al., 2012). This protein inserts itself into the epithelial cell membrane and facilitates the formation of transmembrane pores which permeabilize the gastric epithelium to urea (Szabo et al., 1999; Tombola et al., 1999; Jungblut et al., 2000), probably also providing the bacterium with nutrients (De Luca et al., 2004; Manente et al., 2008). It has been demonstrated that VacA overexpression in AGS cells induces a stop of G1 phase of the cell cycle and an increase in the percentage of apoptotic cells by activation of mitochondrial pathway (Manente et al., 2008). It has been shown that *H. pylori* VacA-secreting strains are more common among patients with distal gastric cancer than among patients with gastritis alone (Miehlke et al., 2000; De Luca et al., 2004). It is well known that *H. pylori* infection causes chronic oxidative stress on gastric mucosa, thereby causing mucosal damage and retarding mucosal repair (Hahm et al., 1998; De Luca and Iaquinto, 2004). Although host cells act to protect themselves against chronic oxidative stress by enhancing activities of antioxidant enzymes (Buommino et al., 2012), it has been demonstrated that HspB interferes with nuclear factor erythroid-2-related factor 2 (Nrf2) pathway that coordinates induction of genes encoding numerous antioxidant and phase II detoxifying enzymes and related proteins (Buommino et al., 2012). Particularly, HspB stabilizes the complex among Nrf2 and its repressor molecule Keap 1 (Kelch-like ECH-associated protein 1), so impeding the translocation of Nrf2 into the nucleus and the consequent activation of ARE gene transcription. Consequently, *H. pylori*-infected cells are impeded to activate the antioxidant response (Buommino et al., 2012). Moreover, co-expression of CagA and HspB in AGS cells is able to induce cell cycle proliferation through an increase of rate of transit between the S/G2-M phase of the cell cycle associated with a specific increase in cyclin D3 and Retinoblastoma gene product, Rb, in its phosphorylated form (De Luca et al., 2003, 2008). Hence, HspB deserves great attention since it has been demonstrated that its activity increases the risk of gastric carcinoma (Iaquinto et al., 2000).

The *H. pylori*-infected stomach displays dramatic morphological changes in the cytoskeleton (Osman et al., 2013). Several studies point their attention on the preventing of cell migration by *H. pylori* by subverting the dynamics of focal adhesions (FAs) (Tsutsumi et al., 2006; Schneider et al., 2008) in order to maintain non-polarized, but immotile, phenotype with reduced acid secretion, as a refuge (Osman et al., 2013). It has been demonstrated that bacterial infection increases IQGAP1 transcript level involved in cell polarity, growth, and proliferation (Conlin et al., 2004; Osman et al., 2013). The increase of IQGAP1 expression level enhances IQGAP1's serine phosphorylation and binding to activated Cdc42-GTP (Rittmeyer et al., 2008) and promotes cell migration and invasion (Wang et al., 2009). Once activated, IQGAP1-Cdc42 complex dissociates adherent junctions (AJs) by delocalizing α-catenin from E-cadherin–α-catenin–β-catenin complex, leading to translocation of β-catenin to the nucleus and onset of oncogenic transcriptional events responsible of cell scattering, increasing migration, and invasion (Noritake et al., 2005; Osman et al., 2013). In addition, *H. pylori* infection promotes gastric epithelial cells invasion by activating metalloproteinases (MMP), important in tissue destruction and remodeling (Wu et al., 2005). Particularly, HspB induces a strong increase in MMP3 and MMP7 (Buommino et al., 2012). MMP7 influences cellular proliferation and apoptosis and is overexpressed in gastric malignancies (Honda et al., 1996). Increased MMP7 secretion has been reported in the gastric epithelial cells of patients infected with *H. pylori*, relative to subjects with *H. pylori* negative dyspepsia (Wroblewski et al., 2003; Sampieri, 2013). Moreover, it has been observed that migration is greater in cells belonging to *H. pylori* positive subjects, compared with *H. pylori* negative subjects (Wroblewski et al., 2003; Sampieri, 2013). It has been suggested that overexpression of MMP1 (Wu et al., 2006) and MMP7 (Crawford et al., 2003; Ogden et al., 2008) is dependent upon the pathogenicity island of *H. pylori* (Sampieri, 2013). Moreover, *H. pylori* strongly increases enzymatic activity of MM9 and induces its secretion via NF-κB (Wu et al., 2005; Nam et al., 2011), COX-2 (Wu et al., 2005), and ERK (Nam et al., 2011).

Epigenetic modifications of gastric epithelial cells induced by *H. pylori*

H. pylori-induced GC is an example of inflammation-associated malignancy. This condition is associated with DNA methylation (Alvarez et al., 2013a). Several studies have demonstrated a close association between *H. pylori* infection and aberrant CpG island methylation (Chan et al., 2003; Maekita et al., 2006; Nakajima et al., 2009). During the Correa's cascade, promoter hypermethylation is a commonly observed epigenetic change in major tumor suppressor genes (Wang et al., 2014). Epigenetic mechanisms may operate at gene-specific level in order to regulate gene expression, the maintenance of DNA integrity and stability (Alvarez et al., 2013b). These processes include both chromatin modifications, orchestrated by chromatin-remodeling complexes and histone-modifying enzymes, and DNA methylation, directed by DNA methyltransferase (for review see Chiariotti et al., 2013). Although the mechanism of induction of DNA methylation by *H. pylori* is unknown, it is believed that *H. pylori* possess multiple DNA methyltransferase in T4SS that can directly induce gene methylation in epithelial cells (Wang et al., 2014). Aberrant methylation-induced silencing also occurs in several tumor suppressor genes such as those involved in cell adhesion (E-cadherin) (Grady et al., 2000;

Tamura et al., 2000; Chiariotti et al., 2013), and several other genes, including those related to cell growth control (p16, p14, and APC), DNA repair (mismatch repair gene – hMLH1; BRCA1, MGMT) (Liu et al., 2012; Loh et al., 2012; Cheng et al., 2013; Chiariotti et al., 2013; Wang et al., 2014). These changes are strongly correlated with increased risk for GC (Wang et al., 2014) since DNA methylation is a potent mechanism for silencing gene expression and maintaining genome stability (Chiariotti et al., 2013). It has been shown that 26 genes were hypermethylated in individuals with current or past *H. pylori* infection (Nakajima et al., 2009; Chiariotti et al., 2013). Recently, it has been demonstrated that prolonged bacterial infections lead to saturation of the repair capabilities of the host cells and thus to an ineffective and mutagenic DNA repair system (Toller et al., 2011; Alvarez et al., 2013b). So, *H. pylori* infection-mediated DNA methylation in adults may depend not only on the level of the inflammatory response but also on the persistence and duration of the infection (Alvarez et al., 2013b).

Until now about 20 microRNAs (miRNAs) have been shown to change in response to *H. pylori* infection (for review see Nishizawa and Suzuki, 2013). Particularly, the miRNAs changed in response to *H. pylori* are involved in different biological processes such as cell cycle progression, apoptosis, proliferation, invasion, metastasis, and immune response (Nishizawa and Suzuki, 2013). Some miRNas such as miR-584 and miR-1290 are upregulated in CagA-transformed cells while others such as let-7, miR6a, and miR-101 are downregulated by CagA (Nishizawa and Suzuki, 2013). This process suggests a new pathogenic mechanism for CagA.

Conclusions

Several studies have been published in the last years about mechanisms of *H. pylori* infection. They point their attention on the particular bacterial strategy that aims to avoid and/or combat a negative response by host-infected cells. *H. pylori* is able to integrate inside epithelial gastric cells in order to induce the most favorable conditions for its colonization and growth. The knowledge of molecular mechanisms of bacterial infections may help to realize an early eradication and therapy.

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Literature Cited

Alm RA, Trust TJ. 1999. Analysis of the genetic diversity of *Helicobacter pylori*: The tale of two genomes. J Mol Med 77:834–846.

Alvarez MC, Ladeira MS, Scaletsky IC, Pedrazzoli J, Jr., Ribeiro ML. 2013a. Methylation pattern of THBS1, GATA-4, and HIC1 in pediatric and adult patients infected with *Helicobacter pylori*. Dig Dis Sci 58:2850–2857.

Alvarez MC, Santos JC, Maniezzo N, Ladeira MS, da Silva AL, Scaletsky IC, Pedrazzoli J, Jr., Ribeiro ML. 2013b. MGMT and MLH1 methylation in *Helicobacter pylori*-infected children and adults. World J Gastroenterol 19:3043–3051.

Aspholm M, Olfat FO, Norden J, Sonden B, Lundberg C, Sjostrom R, Altraja S, Odenbreit S, Haas R, Wadstrom T, Engstrand L, Semino-Mora C, Liu H, Dubois A, Teneberg S, Arnqvist A, Boren T. 2006. SabA is the *H. pylori* hemagglutinin and is polymorphic in binding to sialylated glycans. PLoS Pathog 2:e110.

Baik SC, Kim KM, Song SM, Kim DS, Jun JS, Lee SG, Song JY, Park JU, Kang HL, Lee WK, Cho MJ, Youn HS, Ko GH, Rhee KH. 2004. Proteomic analysis of the sarcosine-insoluble outer membrane fraction of *Helicobacter pylori* strain 26695. J Bacteriol 186:949–955.

Bhaskar KR, Garik P, Turner BS, Bradley JD, Bansil R, Stanley HE, LaMont JT. 1992. Viscous fingering of HCl through gastric mucin. Nature 360:458–461.

Blaser MJ, Berg DE. 2001. *Helicobacter pylori* genetic diversity and risk of human disease. J Clin Invest 107:767–773.

Bonis M, Ecobichon C, Guadagnini S, Prévost M-C, Boneca IG. 2010. A M23B family metallopeptidase of *Helicobacter pylori* required for cell shape, pole formation and virulence. Mol Microbiol 78:809–819.

Boreiri M, Samadi F, Etemadi A, Babaei M, Ahmadi E, Sharifi AH, Nikmanesh A, Houshiar A, Pourfarzai F, Yazdanbod A, Alimohammadian M, Sotoudeh M. 2013. Gastric cancer mortality in a high incidence area: Long-term follow-up of *Helicobacter pylori*-related precancerous lesions in the general population. Arch Iran Med 16:343–347.

Buommino E, Donnarumma G, Manente L, De Filippis A, Silvestri F, Iaquinto S, Tufano MA, De Luca A. 2012. The *Helicobacter pylori* protein HspB interferes with Nrf2/Keap1 pathway altering the antioxidant response of Ags cells. Helicobacter 17:417–425.

Buti L, Spooner E, Van der Veen AG, Rappuoli R, Covacci A, Ploegh HL. 2011. *Helicobacter pylori* cytotoxin-associated gene A (CagA) subverts the apoptosis-stimulating protein of p53 (ASPP2) tumor suppressor pathway of the host. Proc Natl Acad Sci USA 108:9238–9243.

Celli JP, Turner BS, Afdhal NH, Keates S, Ghiran I, Kelly CP, Ewoldt RH, McKinley GH, So P, Erramilli S, Bansil R. 2009. *Helicobacter pylori* moves through mucus by reducing mucin viscoelasticity. Proc Natl Acad Sci USA 106:14321–14326.

Censini S, Lange C, Xiang Z, Crabtree JE, Ghiara P, Borodovsky M, Rappuoli R, Covacci A. 1996. cag, a pathogenicity island of *Helicobacter pylori*, encodes type I-specific and disease-associated virulence factors. Proc Natl Acad Sci USA 93:14648–14653.

Chan AO, Lam SK, Wong BC, Wong WM, Yuen MF, Yeung YH, Hui WM, Rashid A, Kwong YL. 2003. Promoter methylation of E-cadherin gene in gastric mucosa associated with *Helicobacter pylori* infection and in gastric cancer. Gut 52:502–506.

Cheng AS, Li MS, Kang W, Cheng VY, Chou JL, Lau SS, Go MY, Lee CC, Ling TK, Ng EK, Yu J, Huang TH, To KF, Chan MW, Sung JJ, Chan FK. 2013. *Helicobacter pylori* causes epigenetic dysregulation of FOXD3 to promote gastric carcinogenesis. Gastroenterology 144:122–133.

Chiariotti L, Angrisano T, Keller S, Florio E, Affinito O, Pallante P, Perrino C, Pero R, Lembo F. 2013. Epigenetic modifications induced by *Helicobacter pylori* infection through a direct microbe-gastric epithelial cells cross-talk. Med Microbiol Immunol 202:327–337.

Cirak MY, Akyon Y, Megraud F. 2007. Diagnosis of *Helicobacter pylori*. Helicobacter 12:4–9.

Conlin VS, Curtis SB, Zhao Y, Moore ED, Smith VC, Meloche RM, Finlay BB, Buchan AM. 2004. *Helicobacter pylori* infection targets adherens junction regulatory proteins and results in increased rates of migration in human gastric epithelial cells. Infect Immun 72:5181–5192.

Correa P. 1992. Human gastric carcinogenesis: A multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res 52:6735–6740.

Crawford HC, Krishna US, Israel DA, Matrisian LM, Washington MK, Peek RM, Jr. 2003. *Helicobacter pylori* strain-selective induction of matrix metalloproteinase-7 in vitro and within gastric mucosa. Gastroenterology 125:1125–1136.

De Luca A, Iaquinto G. 2004. *Helicobacter pylori* and gastric diseases: A dangerous association. Cancer Lett 213:1–10.

De Luca A, Baldi A, Russo P, Todisco A, Altucci L, Giardullo N, Pasquale L, Iaquinto S, D'Onofrio V, Parodi MC, Paggi MG, Iaquinto G. 2003. Coexpression of *Helicobacter pylori*'s proteins CagA and HspB induces cell proliferation in AGS gastric epithelial cells, independently from the bacterial infection. Cancer Res 63:6350–6356.

De Luca A, De Falco M, Iaquinto S, Iaquinto G. 2004. Effects of *Helicobacter pylori* infection on cell cycle progression and the expression of cell cycle regulatory proteins. J Cell Physiol 200:334–342.

De Luca A, De Falco M, Manente L, Dattilo D, Lucariello A, Esposito V, Gnarini M, Citro G, Baldi A, Tufano MA, Iaquinto G. 2008. *Helicobacter pylori* heat shock protein B (HspB) localizes *in vivo* in the gastric mucosa and MALT lymphoma. J Cell Physiol 216:78–82.

Delahay RM, Rugge M. 2012. Pathogenesis of *Helicobacter pylori* infection. Helicobacter 17:9–15.

Demirel BB, Akkas BE, Vural GU. 2013. Clinical factors related with *Helicobacter pylori* infection—Is there an association with gastric cancer history in first-degree family members? Asian Pac J Cancer Prev 14:1797–1802.

Dunn BE, Phadnis SH. 1998. Structure, function and localization of *Helicobacter pylori* urease. Yale J Biol Med 71:63–73.

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

Fox GJ, Wang CT, Parsonnet J. 2006. Helicobacter, chronic inflammation, and cancer. In: Hausen, ZH, editor. Infections, causing human cancer. Hoboken, NJ, USA: Wiley-VCH. pp 386–467.

Gerhard M, Lehn N, Neumayer N, Boren T, Rad R, Schepp W, Miehlke S, Classen M, Prinz C. 1999. Clinical relevance of the *Helicobacter pylori* gene for blood-group antigen-binding adhesin. Proc Natl Acad Sci USA 96:12778–12783.

Gobert AP, Mersey BD, Cheng Y, Blumberg DR, Newton JC, Wilson KT. 2002. Cutting edge: Urease release by *Helicobacter pylori* stimulates macrophage inducible nitric oxide synthase. J Immunol 168:6002–6006.

Goncalves IC, Magalhaes A, Fernandes M, Rodrigues IV, Reis CA, Martins MC. 2013. Bacterial-binding chitosan microspheres for gastric infection treatment and prevention. Acta Biomater 9:9370–9378.

Grady WM, Willis J, Guilford PJ, Dunbier AK, Toro TT, Lynch H, Wiesner G, Ferguson K, Eng C, Park JG, Kim SJ, Markowitz S. 2000. Methylation of the CDH1 promoter as the second genetic hit in hereditary diffuse gastric cancer. Nat Genet 26:16–17.

Hahm KB, Lee KJ, Kim JH, Cho SW, Chung MH. 1998. *Helicobacter pylori* infection, oxidative DNA damage, gastric carcinogenesis, and reversibility by rebamipide Dig Dis Sci 43:72S–77S.

Hnatyszyn A, Wielgus K, Kaczmarek-Rys M, Skrzypczak-Zielinska M, Szalata M, Mikolajczyk-Stecyna J, Stanczyk J, Dziuba I, Mikstacki A, Slomski R. 2013. Interleukin-1 gene polymorphisms in chronic gastritis patients infected with *Helicobacter pylori* as risk factors of gastric cancer development. Arch Immunol Ther Exp 61:503–512.

Honda M, Mori M, Ueo H, Sugimachi K, Akiyoshi T. 1996. Matrix metalloproteinase-7 expression in gastric carcinoma. Gut 39:444–448.

Iaquinto G, Todisco A, Giardullo N, D'Onofrio V, Pasquale L, De Luca A, Andriulli A, Perri F, Rega C, De Chiara G, Landi M, Taccone W, Leandro G, Figura N. 2000. Antibody response to *Helicobacter pylori* CagA and heat-shock proteins in determining the risk of gastric cancer development. Dig Liver Dis 32:378–383.

IARC. 1994. Schistosomes, liver flukes and *Helicobacter pylori*. Monographs on the evaluation of carcinogenic risks to humans. Lion, France: IARC Sci Publ. pp 1–241.

Ilver D, Arnqvist A, Ogren J, Frick IM, Kersulyte D, Incecik ET, Berg DE, Covacci A, Engstrand L, Boren T. 1998. *Helicobacter pylori* adhesin binding fucosylated histo-blood group antigens revealed by retagging. Science 279:373–377.

Jungblut PR, Bumann D, Haas G, Zimny-Arndt U, Holland P, Lamer S, Siejak F, Aebischer A, Meyer TF. 2000. Comparative proteome analysis of *Helicobacter pylori*. Mol Microbiol 36:710–725.

Kang HM, Kim N, Park YS, Hwang JH, Kim JW, Jeong SH, Lee DH, Lee HS, Jung HC, Song IS. 2008. Effects of *Helicobacter pylori* infection on gastric mucin expression. J Clin Gastroenterol 42:29–35.

Kaplan-Turkoz B, Jimenez-Soto LF, Dian C, Ertl C, Remaut H, Louche A, Tosi T, Haas R, Terradot L. 2012. Structural insights into *Helicobacter pylori* oncoprotein CagA interaction with beta1 integrin. Proc Natl Acad Sci USA 109:14640–14645.

Kim N, Marcus EA, Wen Y, Weeks DL, Scott DR, Jung HC, Song IS, Sachs G. 2004. Genes of *Helicobacter pylori* regulated by attachment to AGS cells. Infect Immun 72:2358–2368.

Kocer B, Ulas M, Ustundag Y, Erdogan S, Karabeyoglu M, Yldrm O, Unal B, Cengiz O, Soran A. 2004. A confirmatory report for the close interaction of *Helicobacter pylori* with gastric epithelial MUC5AC expression. J Clin Gastroenterol 38:496–502.
Lee YY, Derakhsham MH. 2013. Environmental and lifestyle risk factors of gastric cancer. Arch Iran Med 16:358–365.
Lillehoj EP, Guang W, Ding H, Czinn SJ, Blanchard TG. 2012. *Helicobacter pylori* and gastric inflammation: Role of MUC1 mucin. J Pediatr Biochem 2:125–132.
Ling F, Wang X, Dai D, Yu M, Chen C, Qian J, Liu C, Zhang Y, Ding J, Guan XW, Shao S. 2013. The *Helicobacter pylori* protein CagM is located in the transmembrane channel that is required for CagA translocation. Curr Microbiol 67:531–536.
Liu JB, Wu XM, Cai J, Zhang JY, Zhang JL, Zhou SH, Shi MX, Qiang FL. 2012. CpG island methylator phenotype and *Helicobacter pylori* infection associated with gastric cancer. World J Gastroenterol 18:5129–5134.
Logan RP, Walker MM. 2001. ABC of the upper gastrointestinal tract: Epidemiology and diagnosis of *Helicobacter pylori* infection. BMJ 323:920–922.
Loh JT, Friedman DB, Piazuelo MB, Bravo LE, Wilson KT, Peek RM, Jr., Correa P, Cover TL. 2012. Analysis of *Helicobacter pylori* cagA promoter elements required for salt-induced upregulation of CagA expression. Infect Immun 80:3094–3106.
Lu XX, Yu JL, Ying LS, Han J, Wang S, Yu QM, Wang XB, Fang XH, Ling ZQ. 2012. Stepwise cumulation of RUNX3 methylation mediated by *Helicobacter pylori* infection contributes to gastric carcinoma progression. Cancer 118:5507–5517.
Machado JC, Nogueira AM, Carneiro F, Reis CA, Sobrinho-Simoes M. 2000. Gastric carcinoma exhibits distinct types of cell differentiation: An immunohistochemical study of trefoil peptides (TFF1 and TFF2) and mucins (MUC1, MUC2, MUC5AC, and MUC6). J Pathol 190:437–443.
Maekita T, Nakazawa K, Mihara M, Nakajima T, Yanaoka K, Iguchi M, Arii K, Kaneda A, Tsukamoto T, Tatematsu M, Tamura G, Saito D, Sugimura T, Ichinose M, Ushijima T. 2006. High levels of aberrant DNA methylation in *Helicobacter pylori*-infected gastric mucosae and its possible association with gastric cancer risk. Clin Cancer Res 12:989–995.
Mahdavi J, Sonden B, Hurtig M, Olfat FO, Forsberg L, Roche N, Angstrom J, Larsson T, Teneberg S, Karlsson KA, Altraja S, Wadstrom T, Kersulyte D, Berg DE, Dubois A, Petersson C, Magnusson KE, Norberg T, Lindh F, Lundskog BB, Arnqvist A, Hammarstrom L, Boren T. 2002. *Helicobacter pylori* SabA adhesin in persistent infection and chronic inflammation. Science 297:573–578.
Manente L, Perna A, Buommino E, Altucci L, Lucariello A, Citro G, Baldi A, Iaquinto G, Tufano MA, De Luca A. 2008. The *Helicobacter pylori*'s protein VacA has direct effects on the regulation of cell cycle and apoptosis in gastric epithelial cells. J Cell Physiol 214: 582–587.
Marques T, David L, Reis C, Nogueira A. 2005. Topographic expression of MUC5AC and MUC6 in the gastric mucosa infected by *Helicobacter pylori* and in associated diseases. Pathol Res Pract 201:665–672.
Melton SD, Genta RM, Souza RF. 2010. Biomarkers and molecular diagnosis of gastrointestinal and pancreatic neoplasms. Nat Rev Gastroenterol Hepatol 7:620–628.
Miehlke S, Kirsch C, Agha-Amiri K, Gunther T, Lehn N, Malfertheiner P, Stolte M, Ehninger G, Bayerdorffer E. 2000. The *Helicobacter pylori* vacA s1, m1 genotype and cagA is associated with gastric carcinoma in Germany. Int J Cancer 87:322–327.
Montecucco C, Papini E, de Bernard M, Zoratti M. 1999. Molecular and cellular activities of *Helicobacter pylori* pathogenic factors. FEBS Lett 452:16–21.
Mueller D, Tegtmeyer N, Brandt S, Yamaoka Y, De Poire E, Sgouras D, Wessler S, Torres J, Smolka A, Backert S. 2012. c-Src and c-Abl kinases control hierarchic phosphorylation and function of the CagA effector protein in Western and East Asian *Helicobacter pylori* strains. J Clin Invest 122:1553–1566.
Nakajima N, Ito Y, Yokoyama K, Uno A, Kinukawa N, Nemoto N, Moriyama M. 2009. The expression of murine double minute 2 (MDM2) on *Helicobacter pylori*-infected intestinal metaplasia and gastric cancer. J Clin Biochem Nutr 44:196–202.
Nam YH, Ryu E, Lee D, Shim HJ, Lee YC, Lee ST. 2011. CagA phosphorylation-dependent MMP-9 expression in gastric epithelial cells. Helicobacter 16:276–283.
Nishizawa T, Suzuki H. 2013. The role of microRNA in gastric malignancy. Int J Mol Sci 14:9487–9496.
Nomura S, Baxter T, Yamaguchi H, Leys C, Vartapetian AB, Fox JG, Lee JR, Wang TC, Goldenring JR. 2004. Spasmolytic polypeptide expressing metaplasia to preneoplasia in *H. felis*-infected mice. Gastroenterology 127:582–594.
Noritake J, Watanabe T, Sato K, Wang S, Kaibuchi K. 2005. IQGAP1: A key regulator of adhesion and migration. J Cell Sci 118:2085–2092.
Noto JM, Peek RM, Jr. 2012. *Helicobacter pylori*: An overview. Methods Mol Biol 921:7–10.
Ogden SR, Wroblewski LE, Weydig C, Romero-Gallo J, O'Brien DP, Israel DA, Krishna US, Fingleton B, Reynolds AB, Wessler S, Peek RM, Jr. 2008. p120 and Kaiso regulate *Helicobacter pylori*-induced expression of matrix metalloproteinase-7. Mol Biol Cell 19:4110–4121.
Osman MA, Bloom GS, Tagoe EA. 2013. *Helicobacter pylori*-induced alteration of epithelial cell signaling and polarity: a possible mechanism of gastric carcinoma etiology and disparity. Cytoskeleton 70:349–359.
O'Toole PW, Lane MC, Porwollik S. 2000. *Helicobacter pylori* motility. Microbes Infect 2:1207–1214.
Parreira P, Magalhaes A, Reis CA, Boren T, Leckband D, Martins MC. 2013. Bioengineered surfaces promote specific protein-glycan mediated binding of the gastric pathogen *Helicobacter pylori*. Acta Biomater 9:8885–8893.
Penta R, De Falco M, Iaquinto G, De Luca A. 2005. *Helicobacter pylori* and gastric epithelial cells: From gastritis to cancer. J Exp Clin Cancer Res 24:337–345.
Perrais M, Rousseaux C, Ducourouble MP, Courcol R, Vincent P, Jonckheere N, Van Seuningen I. 2014. *Helicobacter pylori* urease and flagellin alter mucin gene expression in human gastric cancer cells. Gastric Cancer 17:235–246.
Phadnis SH, Parlow MH, Levy M, Ilver D, Caulkins CM, Connors JB, Dunn BE. 1996. Surface localization of *Helicobacter pylori* urease and a heat shock protein homolog requires bacterial autolysis. Infect Immun 64:905–912.
Pham KT, Weiss E, Jimenez Soto LF, Breithaupt U, Haas R, Fischer W. 2012. CagI is an essential component of the *Helicobacter pylori* Cag type IV secretion system and forms a complex with CagL. PLoS ONE 7:e35341.
Queiroz DM, Silva CI, Goncalves MH, Braga-Neto MB, Fialho AB, Fialho AM, Rocha GA, Rocha AM, Batista SA, Guerrant RL, Lima AA, Braga LL. 2012. Higher frequency of cagA EPIYA-C phosphorylation sites in *H. pylori* strains from first-degree relatives of gastric cancer patients. BMC Gastroenterol 12:107.
Rittmeyer EN, Daniel S, Hsu SC, Osman MA. 2008. A dual role for IQGAP1 in regulating exocytosis. J Cell Sci 121:391–403.
Saha A, Hammond CE, Beeson C, Peek RM, Jr., Smolka AJ. 2010. *Helicobacter pylori* represses proton pump expression and inhibits acid secretion in human gastric mucosa. Gut 59: 874–881.
Sampieri CL. 2013. *Helicobacter pylori* and gastritis: The role of extracellular matrix metalloproteases, their inhibitors, and the disintegrins and metalloproteases—A systematic literature review. Dig Dis Sci 58:2777–2783.
Schneider S, Weydig C, Wessler S. 2008. Targeting focal adhesions: *Helicobacter pylori*–host communication in cell migration. Cell Commun Signal 6:2.
Shaffer CL, Gaddy JA, Loh JT, Johnson EM, Hill S, Hennig EE, McClain MS, McDonald WH, Cover TL. 2011 *Helicobacter pylori* exploits a unique repertoire of type IV secretion system components for pilus assembly at the bacteria–host cell interface PLoS Pathog 7: e1002237.
Shi D, Qiu XM, Yan XJ. 2014. The changes in MUC5AC expression in gastric cancer before and after *Helicobacter pylori* eradication. Clin Res Hepatol Gastroenterol 38:235–240.
Shiotani A, Cen P, Graham DY. 2013. Eradication of gastric cancer is now both possible and practical. Semin Cancer Biol 23:492–501.
Smolka AJ, Backert S. 2012. How *Helicobacter pylori* infection controls gastric acid secretion. J Gastroenterol 47:609–618.
Sun Y, Li JY, He JS, Zhou LX, Chen K. 2005. Tissue microarray analysis of multiple gene expression in intestinal metaplasia, dysplasia and carcinoma of the stomach. Histopathology 46:505–514.
Szabo I, Brutsche S, Tombola F, Moschioni M, Satin B, Telford JL, Rappuoli R, Montecucco C, Papini E, Zoratti M. 1999. Formation of anion-selective channels in the cell plasma membrane by the toxin VacA of *Helicobacter pylori* is required for its biological activity. EMBO J 18:5517–5527.
Tamura G, Yin J, Wang S, Fleisher AS, Zou T, Abraham JM, Kong D, Smolinski KN, Wilson KT, James SP, Silverberg SG, Nishizuka S, Terashima M, Motoyama T, Meltzer SJ. 2000. E-cadherin gene promoter hypermethylation in primary human gastric carcinomas. J Nation Cancer Inst 92:569–573.
Tegtmeyer N, Wessler S, Backert S. 2011. Role of the cag-pathogenicity island encoded type IV secretion system in *Helicobacter pylori* pathogenesis. FEBS J 278:1190–1202.
Toller IM, Neelsen KJ, Steger M, Hartung ML, Hottiger MO, Stucki M, Kalali B, Gerhard M, Sartori AA, Lopes M, Muller A. 2011. Carcinogenic bacterial pathogen *Helicobacter pylori* triggers DNA double-strand breaks and a DNA damage response in its host cells. Proc Natl Acad Sci USA 108:14944–14949.
Tomb JF, White O, Kerlavage AR, Clayton RA, Sutton GG, Fleischmann RD, Ketchum KA, Klenk HP, Gill S, Dougherty BA, Nelson K, Quackenbush J, Zhou L, Kirkness EF, Peterson S, Loftus B, Richardson D, Dodson R, Khalak HG, Glodek A, McKenney K, Fitzegerald LM, Lee N, Adams MD, Hickey EK, Berg DE, Gocayne JD, Utterback TR, Peterson JD, Kelley JM, Cotton MD, Weidman JM, Fujii C, Bowman C, Watthey L, Wallin E, Hayes WS, Borodovsky M, Karp PD, Smith HO, Fraser CM, Venter JC. 1997. The complete genome sequence of the gastric pathogen *Helicobacter pylori.* Nature 388: 539–547.
Tombola F, Carlesso C, Szabo I, de Bernard M, Reyrat JM, Telford JL, Rappuoli R, Montecucco C, Papini E, Zoratti M. 1999. *Helicobacter pylori* vacuolating toxin forms anion-selective channels in planar lipid bilayers: Possible implications for the mechanism of cellular vacuolation. Biophys J 76:1401–1409.
Tsutsumi R, Takahashi A, Azuma T, Higashi H, Hatakeyama M. 2006. Focal adhesion kinase is a substrate and downstream effector of SHP-2 complexed with *Helicobacter pylori* CagA. Mol Cell Biol 26:261–276.
Van de Bovenkamp JH, Mahdavi J, Korteland-Van Male AM, Buller HA, Einerhand AW, Boren T, Dekker J. 2003. The MUC5AC glycoprotein is the primary receptor for *Helicobacter pylori* in the human stomach. Helicobacter 8:521–532.
Van den Brink GR, Tytgat KM, Van der Hulst RW, Van der Loos CM, Einerhand AW, Buller HA, Dekker J. 2000. *H. pylori* colocalises with MUC5AC in the human stomach Gut 46:601–607.
Vanet A, Labigne A. 1998. Evidence for specific secretion rather than autolysis in the release of some *Helicobacter pylori* proteins. Infect Immun 66:1023–1027.
Wang AY, Peura DA. 2011. The prevalence and incidence of *Helicobacter pylori*-associated peptic ulcer disease and upper gastrointestinal bleeding throughout the world. Gastrointest Endosc Clin N Am 21:613–635.
Wang JB, Sonn R, Tekletsadik YK, Samorodnitsky D, Osman MA. 2009. IQGAP1 regulates cell proliferation through a novel CDC42-mTOR pathway. J Cell Sci 122:2024–2033.
Wang F, Meng W, Wang B, Qiao L. 2014. *Helicobacter pylori*-induced gastric inflammation and gastric cancer. Cancer Lett 345:196–202.
Weeks DL, Eskandari S, Scott DR, Sachs G. 2000. A H+-gated urea channel: The link between *Helicobacter pylori* urease and gastric colonization. Science 287:482–485.
Wiedemann T, Hofbaur S, Tegtmeyer N, Huber S, Sewald N, Wessler S, Backert S, Rieder G. 2012. *Helicobacter pylori* CagL dependent induction of gastrin expression via a novel alphavbeta5-integrin-integrin linked kinase signalling complex. Gut 61:986–996.
Wroblewski LE, Noble PJ, Pagliocca A, Pritchard DM, Hart CA, Campbell F, Dodson AR, Dockray GJ, Varro A. 2003. Stimulation of MMP-7 (matrilysin) by *Helicobacter pylori* in human gastric epithelial cells: Role in epithelial cell migration. J Cell Sci 116:3017–3026.
Wu CY, Wang CJ, Tseng CC, Chen HP, Wu MS, Lin JT, Inoue H, Chen GH. 2005 *Helicobacter pylori* promote gastric cancer cells invasion through a NF-kappaB and COX-2-mediated pathway World J Gastroenterol 11:3197–3203.
Wu JY, Lu H, Sun Y, Graham DY, Cheung HS, Yamaoka Y. 2006. Balance between polyoma enhancing activator 3 and activator protein 1 regulates *Helicobacter pylori*-stimulated matrix metalloproteinase 1 expression. Cancer Res 66:5111–5120.
Xu X, Liu Z, Fang M, Yu H, Liang X, Li X, Liu X, Chen C, Jia J. 2012. *Helicobacter pylori* CagA induces ornithine decarboxylase upregulation via Src/MEK/ERK/c-Myc pathway: Implication for progression of gastric diseases. Exp Biol Med 237:435–441.
Yamaoka Y, Souchek J, Odenbreit S, Haas R, Arnqvist A, Boren T, Kodama T, Osato MS, Gutierrez O, Kim JG, Graham DY. 2002. Discrimination between cases of duodenal ulcer and gastritis on the basis of putative virulence factors of *Helicobacter pylori*. J Clin Microbiol 40:2244–2246.