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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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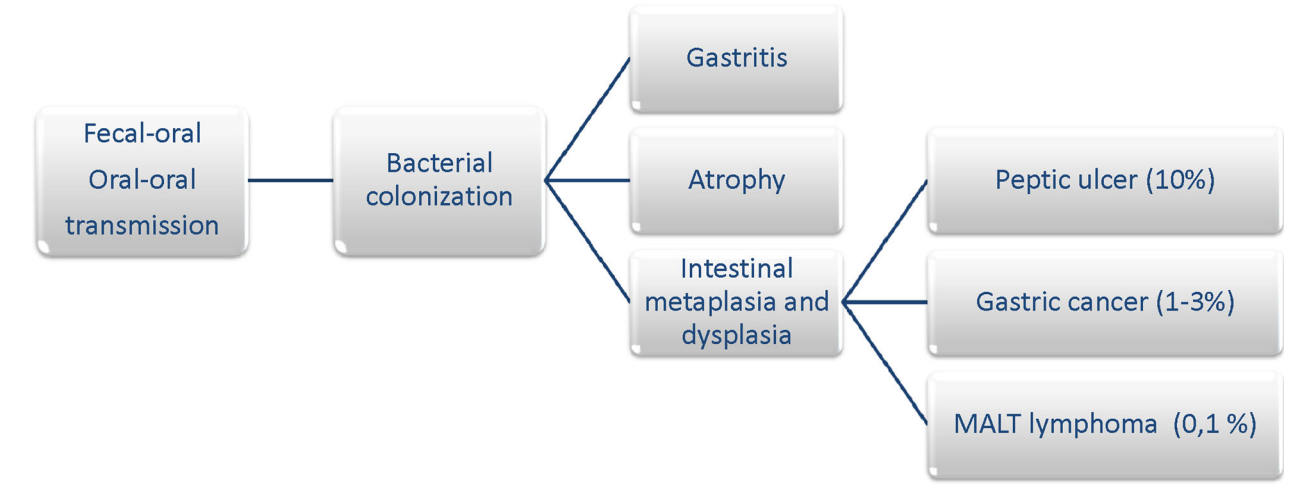

Fig. 1. Sequence of subsequent events from bacterial transmission to the host until precancerous and gastric lesions induced by *H. pylori*.

(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;

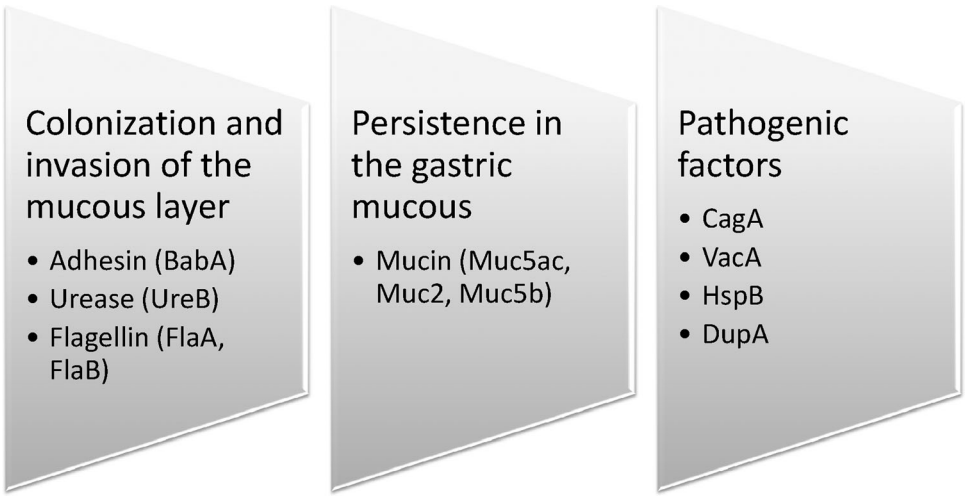

Fig. 2. Schematic representation of some bacterial factors involved in different stages of *H. pylori* pathogenicity.

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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