

CAG PATHOGENICITY ISLAND OF *Helicobacter pylori* AND ITS ASSOCIATION TO PRENEOPLASTIC LESIONS AND GASTRIC CANCER

EL ISLOTE DE PATOGENICIDAD CAG DE *Helicobacter pylori* Y SU ASOCIACIÓN CON LESIONES PRENEOPLÁSICAS Y CÁNCER GÁSTRICO

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ABSTRACT

Gastric cancer is one of the main causes of death by cancer in the world and the infection with *Helicobacter pylori* is one of the main risk factors associated with its appearance. *Helicobacter pylori* is a bacterium that colonizes the gastric mucosa, infecting about half of the world's population. The pathological effects caused by infections with *H. pylori* greatly depend on an IV type secretion system encoded in the *cag* pathogenicity island (*cagPAI*). In this review, we describe the composition of the *cagPAI*, the alterations of cellular signaling pathways mediated by *cagPAI* which regulate oncogenic cellular responses that may increase the risk of malignant transformation associated with the infection and the importance of polymorphisms in *cagPAI* genes as potential markers of progression to gastric cancer.

Keywords: stomach cancer, genomic islands, precancerous condition, genetic.

RESUMEN

El cáncer gástrico es una de las principales causas de muerte por cáncer en el mundo y la infección con *Helicobacter pylori* es uno de los principales factores de riesgo, asociados a su aparición. *H. pylori* es una bacteria que coloniza la mucosa gástrica, infectando alrededor de la mitad de la

población mundial. Los efectos patológicos ocasionados por la infección con *H. pylori* dependen, en buena parte, de un sistema de secreción tipo IV, codificado en el islote de patogenicidad *cag* (*cagPAI*). En esta revisión, se describe la composición del *cagPAI*, la alteración de las vías de señalización celular mediadas por el *cagPAI*, que regulan respuestas celulares oncogénicas, que pueden incrementar el riesgo de transformación maligna asociada a la infección y la importancia de los polimorfismos en genes del *cagPAI*, como posibles marcadores de progresión a cáncer gástrico.

Palabras clave: cáncer de estómago, islas genómicas, condición precancerosa.

INTRODUCTION

Gastric cancer is fifth in occurrence worldwide after breast, lung, colorectal, and prostate cancers (<http://globocan.iarc.fr/Default.aspx>). In 2012, there were 951,594 new cases of gastric cancer reported in the world, which represent 6.8% of the total number of cancer cases; in the Colombian population, we observe an incidence rate of 13.6 cases for every 100.000 inhabitants (<http://globocan.iarc.fr/Default.aspx>). In this same year, 723.073 people with gastric cancer died, a number that represents 8,8% of deaths caused by cancer; the mortality rate in Colombia for that year was 11.3 for every 100.000 inhabitants (<http://globocan.iarc.fr/Default.aspx>).

The highest incidence of gastric cancer can be found in southeast and central Asia, in regions of central Europe and in South America (Nagini, 2012). The occurrence of gastric cancer is between two and four times greater in men than in women, however, the course of the disease is similar in both sexes. Different factors have been associated to a greater risk of developing this pathology, among these is the high levels of salt intake, family history of gastric cancer, poor socioeconomic conditions, ancestry and others, however, the main factor associated with the development of gastric cancer is infection by *H. pylori* (Correa & Houghton, 2007; Dinis-Ribeiro *et al.* 2012). This association was discovered through serology studies of cases and controls, in which it was observed that the presence of *H. pylori* antibodies conferred a risk between 2.1 and 16.7 times greater of developing gastric cancer compared to seronegative individuals (IARC Working Group on the evaluation of Carcinogenic Risks to Humans, 1994). *H. pylori* infects half of the global population with marked differences between regions (Suerbaum & Michetti, 2002). The prevalence of the infection in developed countries is between 20 and 40%, while in developing countries it is closer to 100% (Windsor *et al.* 2005). The bacteria causes gastritis in all the people infected, which may last decades unless the infection is treated, this gastritis can become a peptic ulcer in 10 to 20% of individuals and gastric cancer in 1 to 3% (Kuipers *et al.* 1995). The factors which determine that a subgroup of individuals infected with *H. pylori* develops a serious gastroduodenal disease while the majority remain carriers, are not completely clear. It is believed that it is a combination of environmental factors, the host's genetics and the virulence of the bacteria.

The virulence locus of *H. pylori* most strongly associated with clinical disease compared to the asymptomatic disease is the *cag* pathogenicity island (*cagPAI*) (Yamaoka *et al.* 2008). The purpose of this revision is to describe the *cagPAI* of *H. pylori*, its effects on epithelial cells, variations in its genes and possible usefulness as preneoplastic lesion and gastric cancer markers.

MATERIALS AND METHODS

This is a narrative review, which was prepared by consulting the MEDLINE database between the years 1996 and 2016, using MESH descriptors: *Helicobacter pylori*, genomic islands, CagA protein and stomach cancer. Documents which addressed *H. pylori* generalities, clinical results of infection, epidemiology, pathogenicity island effects in intracellular signaling pathways and polymorphisms in pathogenicity island genes in their content were selected. The search was completed by reading and tracing bibliography referenced in the selected documents.

RESULTS

Helicobacter pylori. *H. pylori* is a gram-negative bacteria that was discovered as the main cause of chronic gastritis by Warren and Marshall in the year 1984, in a project which subsequently led them to become the winners of the Nobel Prize in Medicine, in 2005 (Marshall & Warren, 1984). It is a curved, multi flagellated, bacillary microorganism, which can also appear in coccoid form which is viable but not cultivable and is considered a dormant state (Kusters *et al.* 2006).

This bacteria is capable of surviving in the acid conditions of the stomach due to the action of the urease, an enzyme it has in abundance and which allows it to hydrolyze the gastric urea and produce ammonia (NH₃) alkalinizing the surrounding medium (Miller & Maier, 2014; Smoot *et al.* 1990).

***H. pylori* and gastroduodenal disease.** All the individuals infected with *H. pylori* develop superficial gastritis. In some individuals the gastritis is predominantly in the gastric antrum and is associated with a greater production of hydrochloric acid, it does not imply a greater risk of gastric cancer and is associated with a greater risk of duodenal cancer (Hansson *et al.* 1996). Another group of individuals develops gastritis that is predominantly in the gastric corpus which is associated with hypochlorhydria, gastric atrophy and a greater risk of gastric cancer (Kusters *et al.* 2006). Gastric cancer, specifically the intestinal type, is the result of a series of sequential steps described by pathologist Pelayo Correa, which begin with infection of the gastric mucosa by *H. pylori* and the transition from normal mucosa to chronic superficial gastritis which progresses to atrophic gastritis, intestinal metaplasia, dysplasia and finally gastric adenocarcinoma (Correa, 1996) (Figure 1).

The result of the infection depends on environmental factors, the host and the bacteria. The virulence factor of *H. pylori* that is more strongly associated to clinical disease compared to asymptomatic disease, is the *cagPAI* (Hatakeyama, 2004).

***cag* Pathogenicity Island (*cagPAI*).** Pathogenicity islands (PAI) are genomic elements, which carry one or more virulence genes, and are present in the genome of pathogenic bacteria, but absent in non-pathogenic isolates of the same species, generally occupying relatively big genomic regions, between 100 and 200 kb. The PAI have a percentage of guanine and cytosine different from the genome of the bacteria that carries them. It is considered that these PAI, which obtain the bacteria by horizontal transmission, maintain the basis composition of donor species. They are normally located near transfer RNA genes and are generally flanked by direct repeats (Schmidt & Hensel, 2004).

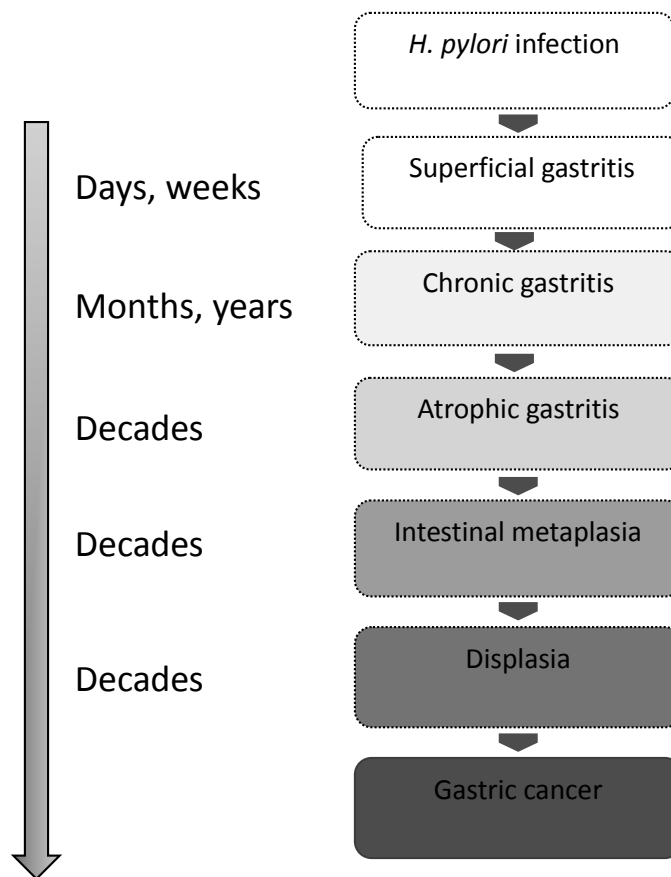


Figure 1. Gastric cancer progression model suggested by Correa (1996).

The pathogenicity island for *H. pylori* was described in 1996, its presence divides strains into two categories: very virulent or type I, which carry the *cagPAI* and mildly virulent or type II which do not carry the *cagPAI* (Censini *et al.* 1996). The *cagPAI* has an approximate size of 40 kb, it is flanked by 31 pb direct repeats, with a 35% content of guanine and cytosine unlike the bacteria which has 39% (Tomb *et al.* 1997), it contains between 27 and 31 genes. It was acquired horizontally by the bacteria, at the integration point of the *cagPAI* in the bacteria there are no transfer RNA genes, the *cagPAI* insertion in the bacteria interrupts the glutamate racemase gene (Akopyants *et al.* 1998; Censini *et al.* 1996). In some strains the *cagPAI* is divided into two segments I (14 genes) and II (16 genes) separated by an IS605 insertion sequence or in a few strains by a chromosomal sequence (Akopyants *et al.* 1998; Censini *et al.* 1996). In figure 2, there is a diagram of the *cagPAI* organization.

The *cagPAI* genes code a type IV secretion system (T4SS), these systems are found in several bacteria, gram-negative as well as gram-positive, are evolutionarily related to DNA

conjugation machineries and are used by pathogenic bacteria such as *Agrobacterium tumefaciens*, *Bartonella*, *Bordetella*, *Helicobacter pylori* and *Legionella* to introduce DNA or proteins into the eukaryotic cells. Consisting of approximately 11 virB proteins codified by virB1 to virB11 genes in the SST4 of the *A. tumefaciens*, considered the prototype (Backert *et al.* 2015; Fischer, 2011). The *cagPAI* shows significant differences to the T4SS of other bacteria, although it contains proteins that have similarities in sequence with all virB proteins, it has five important components that are not similar to any known protein (Backert *et al.* 2015; Fischer, 2011).

In figure 3, there is a diagram with the composition of the T4SS, at least 18 of the *cagPAI* genes code components of the *H. pylori* T4SS (Backert *et al.* 2015; Hagymasi & Tulassay, 2014). The components of this secretion system include: a) Pilus component: CagC, which forms the main extracellular structure that joins with the CagL, CagH, and CagI on the tip to interact with the β 1 integrins; b) CagH, CagM, CagN, CagT, CagV, CagU, CagW, CagX, CagY, Cag δ

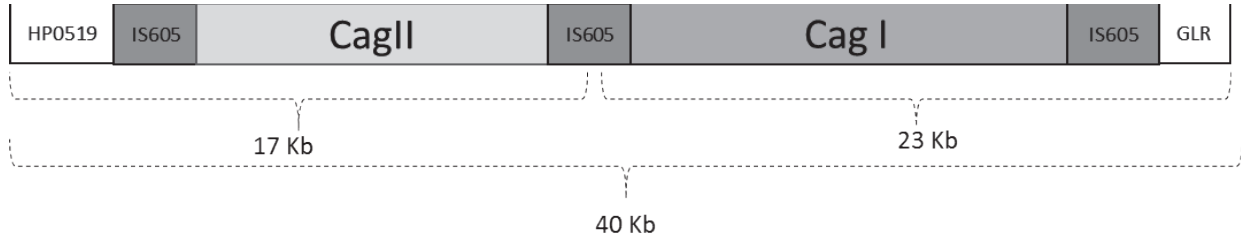


Figure 2. *cag* pathogenicity island structure flanked by *glr* and *Hp0519* genes. The pathogenicity island is divided into two regions (*cagII* and *cagI*) separated by the presence of *IS605* insertion elements. The genes contained code for the type IV secretion system.

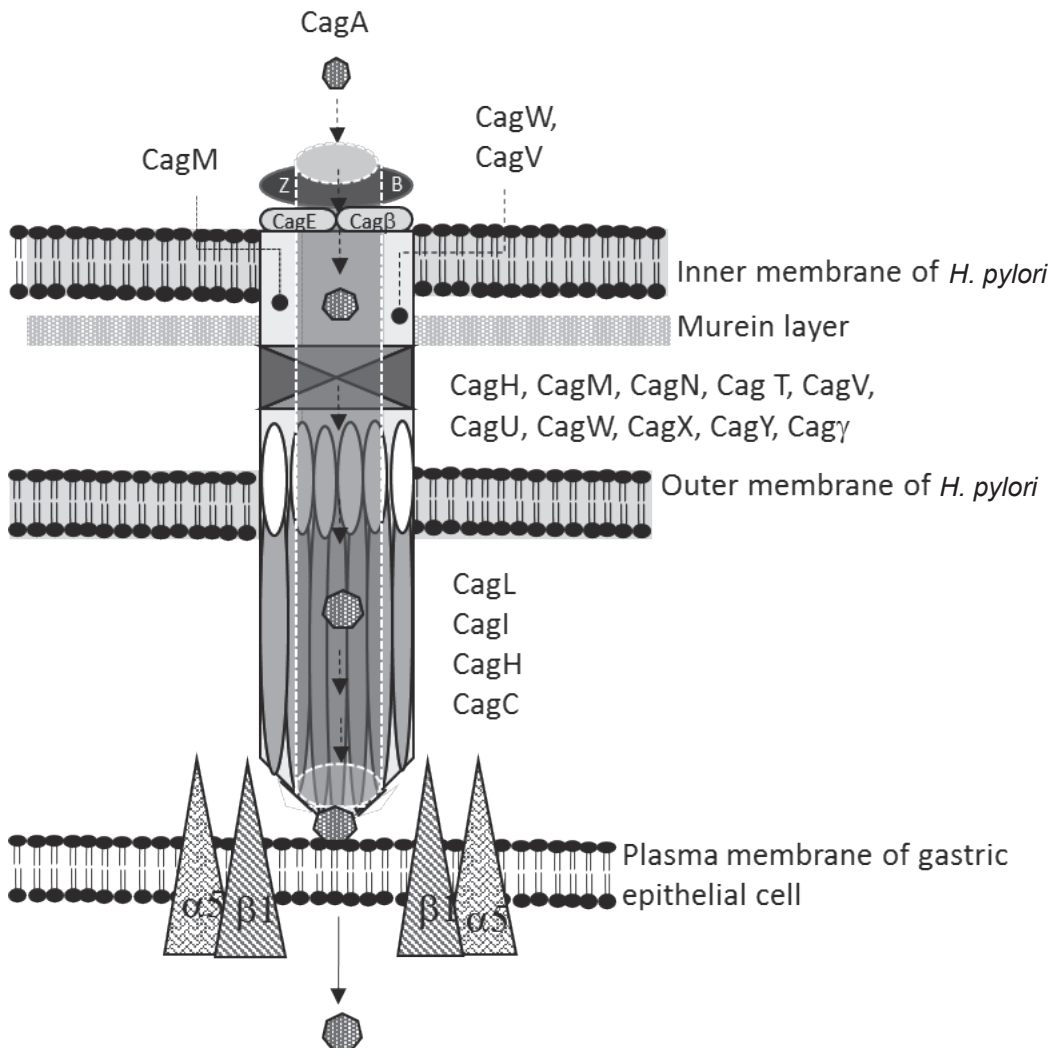


Figure 3. *H. pylori* type IV secretion system structure model. This is a complex formed by proteins encoded in the genes contained in the *cagPAI* of the bacteria that allow *H. pylori* to transfer CagA protein from the bacteria into the gastric epithelial cell.

central complex proteins that form the internal nucleus of the pilus; c) Cag β and CagE energetic factors; that are ATPases that supply the system with energy (Tegtmeyer *et al.* 2011); d) Factors associated to translocation: GagF, CagZ, Cag β . e) Lytic Transglycosylases: Cag γ . f) Substrate: CagA

Alteration of intracellular signaling pathways mediated by the *cagPAI*. The components of the *H. pylori* T4SS assemble to form a needlelike structure that emerges from the surface of the bacteria (Akopyants *et al.* 1998). Upon entering in contact with the epithelial cell, the CagL protein, an important component of the pilus, works as a bacterial adhesin that joins with the $\alpha 5\beta 1$ integrins and activates it (Wiedemann *et al.* 2012). This event allows the transfer of the CagA protein from the bacteria, through the T4SS to the inside of the epithelial cell; where it interacts with about 24 cellular proteins dependently or non-dependently of phosphorylation (Backert *et al.* 2015; Mueller *et al.* 2012; Selbach *et al.* 2009; Tegtmeyer *et al.* 2011). This fact leads to the activation of signaling pathways which promote cellular responses with carcinogenic potential (Hatakeyama, 2004). Once the protein CagA comes into the cell is phosphorylated by Src and Abl kinases (Mueller *et al.* 2012). Phosphorylated CagA activates SHP2 phosphatase which in turn activates Erk 1/2 pathway and causes a reorganization of actin, cell dispersion and cell elongation, morphological changes similar to those caused by growth factors and which have been named hummingbird phenotype (Higashi *et al.* 2002a; Higashi *et al.* 2002b). The phosphorylated CagA protein can join with the Csk kinases and inhibit Src generating a negative circuit, which regulates the amount of phosphorylated CagA (Tsutsumi *et al.* 2003). In addition, the interaction of CagA with SHP2 inactivates the focal adhesion kinase FAK which can activate the Src (Tsutsumi *et al.* 2006).

Non-phosphorylated CagA protein also causes alterations in cell motility and proliferation through the binding to GRB/SOS/RAS and activation of the Raf/MEK/Erk pathway, it also joins with ZO-1 and JAM-A tight junction proteins and the E-cadherin protein of adherens junctions and causes deregulation of junction complexes (Amieva *et al.* 2003; Franco *et al.* 2005). The non-phosphorylated CagA interacts with c-Met and PLC γ phospholipase activating proinflammatory and mitogenic responses (Churin *et al.* 2003), it also joins with the PAR1b cell polarity regulator and inhibits it which induces a loss of cell polarity (Saadat *et al.* 2007). It has recently been described that CagA triggers antiapoptotic responses through the interaction with the p53 stimulating protein and apoptosis (ASPP2) which activates p53 and induces apoptosis after DNA damage, CagA deregulates ASPP2 and causes the degradation of p53 through proteasome (Nesic *et al.* 2014). Another effect mediated by the joining of the T4SS to the cell is the induction of proinflammatory cytokines; once in the cell CagA can

also induce a proinflammatory response which results in the expression of cytokines such as IL-8 through nuclear factor kappa B activation (NF- κ B) (Brandt *et al.* 2005). In addition to CagA, *H. pylori* peptidoglycan can also be introduced in the cell through the T4SS, where it activates the NOD1 and the signaling pathways, which in turn activate NF- κ B and production of proinflammatory cytokines such as IL-8, MIP-2, and type 1 IFN (Viala *et al.* 2004).

Variations in the *cagPAI* Genes. The analysis of the sequence of the entire *cagPAI* for 29 strains from all the known biogeographical regions for *H. pylori*, reported by Olbermann *et al.* (2010), showed that the gene content as well as the organization of the *cagPAI* are well preserved. The diversity seen in *cagPAI* genes mostly consist in synonymous polymorphisms (Olbermann *et al.* 2010). However, some genes coding proteins that are secreted and located on the external part of the bacteria, have a high frequency of non-synonymous polymorphisms, among these are *cagY*, *cagC*, *cagL* y *cagI*. In *cagC* the codons with greater diversification are in amino acids 21 to 42, which are the ones exposed on the surface with highly specific strain epitopes in the N-terminal of the mature CagC protein. The *cagY* gene had variable lengths due to the presence of repetitive modules in the gene.

In a recent study of Rizzato *et al.* (2012), the *cagC*, pilus *cagL*, *cagV*, *cagT* and *cagI* genes of the central complex and *cagE* that encodes one of the enzymes that supply the system with energy, were sequenced. These genes were chosen because their products are essential of the T4SS and some are exposed extracellularly (*cagL* and *cagC*). These genes were sequenced from the DNA obtained from 95 biopsies of Venezuelan and Mexican patients infected with *H. pylori*, diagnosed with gastritis (49 isolations) or gastric cancer (46 isolations). In total 281 variants were found, observed in at least 10% of the samples originally analyzed. Then the frequencies of these genetic variants were compared between the cases of chronic gastritis vs. cases of gastric cancer. Twentysix single nucleotide polymorphisms (SNPs) located in the *cagA*, *cagC*, *cagE*, *cagL*, *cagI* genes were found, 11 synonymous and 14 non-synonymous, which presented significant differences. Two polymorphisms in the *cagE* gene in positions 1039 and 1041 showed a highly significant association to cancer ($p=2,07 \times 10^{-6}$). Since it is possible that the strains from cancer represent simply those capable of surviving in the environment generated by the neoplasia and considering that the gastric cancer arises from a cascade of pre-malignant lesions induced by the infection with *H. pylori*: atrophic gastritis, intestinal metaplasia and dysplasia (Correa & Houghton, 2007); it is very important to evaluate these polymorphisms in samples from different pre-malignant states, and confirm their importance in our population.

cagY is one of the essential genes for T4SS functionality, measured through the ability to induce IL-8. CagY is a 220 Kd protein that is believed to facilitate contact between internal and external parts of the bacterial membrane (Kutter *et al.* 2008). The *cagY* gene has a structure that is not common, with multiple direct repeats of DNA located in a small region of 5' repeats (IRR region) and in a large intermediate region of the gene (MRR region). Possible rearrangements of predicted DNA from these repeats invariably generate in-frame insertions or deletions which result in variant proteins. It has been recently demonstrated that the experimental infection with *H. pylori* in mice or monkeys induces recombinant events in *cagY* dependent on the host's immunity, these changes induced in *cagY* can activate or inactivate the ability of the bacteria to induce IL-8, suggesting that the function of *cagY* diversity is to regulate the activity of the T4SS (Olbermann *et al.* 2010). The characterization of the *cagY* gene in samples from different progression stages of gastric cancer could show us if there are rearrangements in this gene associated with a greater possibility of the infection with *H. pylori* resulting in premalignant lesions and finally leading to gastric cancer.

CagA protein is phosphorylated in various Glu-Pro-Ile-Tyr-Ala (EPIYA) sites present in its C-terminal region (Stein *et al.* 2002). Four types of EPIYA segments have been identified according to the sequences that flank the motifs (EPIYA-A, -B, -C and -D) (Higashi *et al.* 2002a). *H. pylori* isolates of the western hemisphere present the EPIYA-A and EPIYA-B segments followed by a variable number, from 1 to 3, of the EPIYA-C segment. In *H. pylori* from east Asia the CagA protein also presents the EPIYA-A and EPIYA-B segments followed by an EPIYA-D segment, that is only found in Asian isolations (Higashi *et al.* 2002a). However, in western as well as in east Asian strains additional variations in the distribution of the EPIYA segments have been found, in which the A or B segments can be duplicated or absent (ACC, ABCABC, ABDABD) (Naito *et al.* 2006; Reyes-Leon *et al.* 2007). In experiments in which CagA genes with different variants in EPIYA repeats are transferred to AGS epithelial cells, the SHP2 protein has been found to join with EPIYA C and D motifs in a phosphorylation dependent way (Higashi *et al.* 2002a). D motifs have greater affinity by SHP2 than C motifs; however, the greater the number of EPIYA C present in CagA the greater the efficiency in the binding with SHP2 (Higashi *et al.* 2002a). The ability of CagA to deregulate SHP2 seems to be important in determining the oncogenic potential of the strains. In some studies, a greater number of EPIYA-C segments have been observed in CagA protein of isolates from atrophic gastritis and gastric cancer cases compared to isolates from chronic gastritis, suggesting an association between the size of the CagA 3' variable region and the clinical result of the infection (Argent *et al.* 2004; Azuma *et al.* 2002; Basso *et al.* 2008). However, in our studies and

other studies, an association is not confirmed (Acosta *et al.* 2010; Reyes-Leon *et al.* 2007). On the other hand, it has been determined that the ability of CagA to interact with Csk is proportional to the number of EPIYA A and B segments, the capacity of CagA to join Csk attenuates the effects of its interaction with SHP-2 phosphatase and probably reduce its possible oncogenic effects (Naito *et al.* 2006).

DISCUSSION

H. pylori represents a very successful human pathogen with the potential to cause serious diseases in a subgroup of infected individuals. Research on *cagPAI* and CagA protein have led to the knowledge of mechanisms of pathogenesis of the bacteria. Several studies indicate that the CagA protein simulates a eukaryote-signaling factor located in multiprotein complexes or simultaneously in several areas of the infected cell and is capable of joining a number of factors, affecting several signal transduction networks that can have a significant impact on the sequence of the events that lead to gastric cancer.

In our country we have found that *H. pylori* infects over 77% of the adult population (Trujillo *et al.* 2014), despite this high prevalence of the infection, gastric cancer is present in a minimum percentage of the infected population. Therefore, it is important to identify the factors that determine that only a subgroup of infected individuals develops a serious gastroduodenal disease while the majority remain carriers.

In epidemiological studies it has been shown that the infection with *H. pylori* strains that carry the *cagA* gene is associated with a greater risk of developing peptic ulcer and gastric cancer (Yamaoka *et al.* 2008), however, in studies carried out by our group, we have found that 50% of individuals with superficial gastritis in our country are infected with strains that carry the *cagA* gene (Quiroga *et al.* 2005). Therefore, the mere presence of *cagA* gen or *cagPAI* does not allow us to predict the clinical result of the infection, mainly in high risk populations, such as the Colombian population.

Many of the functions of the CagA protein reside in a series of Glu-Pro-Ile-Tyr-Ala amino acid repeat motifs, called EPIYA motif, organized in tandem. Although it has been suggested that the presence of various copies of the type C EPIYA motif is associated with a risk of cancer and with greater activity of CagA *in vitro* (Higashi *et al.* 2002a), there is controversy regarding this (Rizzato *et al.* 2012). We have not found an association between the presence of more type C EPIYA motifs and the risk of gastric cancer in our analyses (Acosta *et al.* 2010; Fajardo *et al.* 2013).

Given the relevance the *cagPAI* has in the biological activities of *H. pylori* which lead to tissue damage, polymorphisms in

the genes that code the proteins which form it, probably play a role as virulence factors. Twentysix polymorphisms have been described in the *cagPAI cagA, cagC, cagE, cagL, cagT, cagV,* and *cagY* genes, which present significant differences in their frequencies between gastric cancer and gastritis. It is important to evaluate these polymorphisms in preneoplastic lesions to examine if these variants also present significant differences in frequency between premalignant lesions and gastritis, so they could be used to identify infected individuals at risk of developing gastric cancer, who would be candidates for eradication.

In conclusion, the study of variations in *cagPAI* genes and their association with the development of preneoplastic lesions and gastric cancer could generate possible molecular markers of *H. pylori* virulence which would allow us to predict the risk of gastric cancer and preneoplastic lesions (atrophic gastritis, intestinal metaplasia, gastric dysplasia).

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