

## Influence of *Helicobacter pylori* oncoprotein CagA in gastric cancer: A critical-reflective analysis

Fabrício Freire de Melo, Hanna Santos Marques, Samuel Luca Rocha Pinheiro, Fabian Fellipe Bueno Lemos, Marcel Silva Luz, Kádima Nayara Teixeira, Cláudio Lima Souza, Márcio Vasconcelos Oliveira

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**Fabrício Freire de Melo, Samuel Luca Rocha Pinheiro, Fabian Fellipe Bueno Lemos, Marcel Silva Luz, Cláudio Lima Souza, Márcio Vasconcelos Oliveira,** Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Vitória da Conquista 45029-094, Brazil

**Hanna Santos Marques,** Campus Vitória da Conquista, Universidade Estadual do Sudoeste da Bahia, Vitória da Conquista 45029-094, Brazil

**Kádima Nayara Teixeira,** Campus Toledo, Universidade Federal do Paraná, Toledo 85919899, Brazil

**Corresponding author:** Fabrício Freire de Melo, PhD, Professor, Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Estrada do Bem Querer, 3293-3391 - Candeias, Vitória da Conquista 45029-094, Brazil. [freiremeloufba@gmail.com](mailto:freiremeloufba@gmail.com)

### Abstract

Gastric cancer is the fifth most common malignancy and third leading cancer-related cause of death worldwide. *Helicobacter pylori* is a Gram-negative bacterium that inhabits the gastric environment of 60.3% of the world's population and represents the main risk factor for the onset of gastric neoplasms. CagA is the most important virulence factor in *H. pylori*, and is a translocated oncoprotein that induces morphofunctional modifications in gastric epithelial cells and a chronic inflammatory response that increases the risk of developing precancerous lesions. Upon translocation and tyrosine phosphorylation, CagA moves to the cell membrane and acts as a pathological scaffold protein that simultaneously interacts with multiple intracellular signaling pathways, thereby disrupting cell proliferation, differentiation and apoptosis. All these alterations in cell biology increase the risk of damaged cells acquiring pro-oncogenic genetic changes. In this sense, once gastric cancer sets in, its perpetuation is independent of the presence of the oncoprotein, characterizing a "hit-and-run" carcinogenic mechanism. Therefore, this review aims to describe *H. pylori*- and CagA-related oncogenic mechanisms, to update readers and discuss the novelties and perspectives in this field.

**Key Words:** *Helicobacter pylori*; Virulence factors; CagA; Gastric cancer; EPIYA motifs; Hit-and-run carcinogenesis

**Core tip:** CagA is a translocated effector protein that induces morphofunctional modifications in gastric epithelial cells and persistent chronic gastric inflammation. Upon translocation, the bacterial oncoprotein acts as a promiscuous scaffold or hub protein, which is capable of disrupting multiple host signaling pathways, thereby inducing precancerous cellular alterations. This review aims to describe *Helicobacter pylori*- and CagA-related oncogenic mechanisms, as well as to discuss the novelties and perspectives in this field.

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## INTRODUCTION

The multiple virulence mechanisms of *Helicobacter pylori* confer an ability to colonize the hostile gastric environment[1]. This pathogen infects > 50% of the global population and is a major health concern due to the serious repercussions related to its colonization[2]. Among the diseases predisposed by *H. pylori* infection, gastric adenocarcinoma is the fifth most common malignancy and third leading cancer-related cause of death worldwide[3]. Of note, the close relationship between *H. pylori* and gastric cancer has led the World Health Organization International Agency for Research on Cancer Working Group to consider the bacterium as a class 1 carcinogen based on epidemiological evidence and biological plausibility[4].

Various virulence factors contribute to successful *H. pylori* colonization and pathogenicity[5]. Among these factors is *cagA*, a well-known gene that encodes an oncogenic protein that seems to be a determining agent in *H. pylori*-related gastric carcinogenesis[6]. CagA seropositivity, regardless of *H. pylori* status, is associated with increased gastric cancer risk. The *cagA* gene is located in the pathogenicity island *cag* (*cagPAI*), a nucleic acid sequence that encodes the type IV secretion system (T4SS), which is a bacterial apparatus that delivers the CagA protein and peptidoglycans into gastric epithelial cells. Inside host cells, that virulence factor suffers phosphorylation at a Glu-Pro-Ile-Tyr-Ala (EPIYA) motif, a variable C-terminal region and, subsequently, promotes the activation of the SH2-containing protein tyrosine phosphatase (SHP2)[7,8]. SHP2, in turn, triggers various mechanisms that lead to important cell changes, including alterations in cellular morphology through the disturbing of cell polarity, which leads to a “hummingbird” phenotype, as well as carcinogenesis-related changes in cytoskeleton[9].

Despite the extensive number of studies on the relationship between CagA and *H. pylori* infection, much still has to be done in order to better understand the role of this oncoprotein in gastric carcinogenesis. Recent investigations have explored multiple host-pathogen interactions in this setting and found other CagA-triggered pathways that probably influence cancer development[10]. Moreover, the action of small RNAs in CagA post-transcriptional regulation has been investigated, showing a broad field to be explored[11]. This review aims to describe *H. pylori*- and CagA-related oncogenic mechanisms, and to discuss the novelties and perspectives in this field.

## PATHOGENESIS OF *H. PYLORI* GASTRIC INFECTION

The capacity to resist severe stomach acid conditions is a notable aspect of *H. pylori*. To provide successful colonization, the pathogen uses various mechanisms, such as enhanced motility, adherence to gastric epithelial cells, enzymatic machinery, and virulence factors[12]. Besides that, the host immune system also plays an essential role during the infection, mainly by a Th1 response against the bacteria [13].

The bacterial flagella are crucial for reaching the protective mucus layer at the exterior of the gastric mucosa. After entering the stomach, *H. pylori* uses its flagella for swimming in gastric content, allowing the pathogen to arrive at the mucus layer[14]. Some studies have shown that the ferric uptake regulator performs an important role in bacterial colonization, positively regulating the flagellar motility switch in *H. pylori* strain J99[15]. Another factor described as a motility modulator is HP0231, a Dsb-like protein. It cooperates in redox homeostasis and is fundamental for gastric establishment[16].

*H. pylori* also depends on chemotaxis for its colonization. The essential pathogen chemoreceptors are T1pA, B, C, D, a CheA kinase, a CheY responsive regulator, and numerous coupling proteins, playing a pivotal role in bacterial pathogenesis[17]. The aggregation of the coupling proteins CheW and CheV1 culminates in the formation of the CheA chemotaxis complex, activating CheA kinase and optimizing the chemotaxis function[18].

An ideal balance between nickel absorption and incorporation is indispensable for *H. pylori* colonization, since nickel is an essential metal for bacterial survival and infection[12,19]. This metal is a cofactor for two significant enzymes: urease and hydrogenase. Both of them have a role in gastric infection, contributing, respectively, to bacterial colonization and metabolism signaling cascade to produce energy[20,21].

Adherence and outer membrane gastric cell receptors are also relevant in bacterial pathogenesis. The blood group antigen binding adhesin (BabA) is the best-studied molecule of *H. pylori*[22]. This protein sequence affects acid sensitivity and plays a critical role in bacterial acid adaptation during infection [12]. Pathogens with high BabA expression levels have increased virulence, leading to duodenal cancer and gastric adenocarcinoma[23]. Another adhesin has been described: HopQ. This molecule binds to cell adhesion molecules related to the carcinoembryonic antigen (carcinoembryonic antigen-related cell adhesion molecules, CEACAMs) 1, 3, 5 and 6, promoting cell signaling guided by this interaction, allowing the translocation of the oncoprotein CagA, the most important *H. pylori* virulence factor, and rising proinflammatory mediators in the infected cells[24,25].

Additionally, besides CagA, a wide range of virulence factors like vacuolating cytotoxin A (VacA), DupA and OipA have been reported as determinant molecules for *H. pylori* pathogenicity[26]. VacA, whose gene is found in most bacterial strains, promotes the formation of acidic vacuoles in gastric epithelial cells and modulate the immune response, leading to an immune tolerance and enduring *H. pylori* infection, due to its role in the activity of T cells and antigen-presenting cells [27,28]. These VacA functions can lead to gastritis and duodenal ulcer and gastric cancer development. The bacterial protein DupA provides acid resistance to the pathogen, and seems to cooperate with the production of interleukin (IL)-8, enhancing its levels in the gastric mucosa[29]. The outer membrane protein OipA contributes to the adhesion and activation of IL-8 production, increasing inflammation. OipA is a significant virulence factor on the infection outcome, resulting in increased development of gastric cancer and peptic ulcers[30].

*H. pylori* infection produces complex host immune responses, through diverse immune mechanisms [31]. During the first contact with the bacteria, a wide range of antigens like lipoteichoic acid and other lipoproteins bind to stomach cell receptors, known as Toll-like receptors (TLRs)[32]. After this interaction, NF- $\kappa$ B and c-Jun N-terminal kinase activation takes place, among the proinflammatory cytokine release as signaling pathways[33]. Neutrophils and mononuclear cells infiltrate the gastric surface, producing nitric oxide and reactive oxygen species (ROS), and recruiting CD4<sup>+</sup> and CD8<sup>+</sup> T cells [34]. Finally, a Th1-polarized response occurs, with enhanced levels of IFN- $\gamma$ , IL-1 $\beta$ , IL-6, IL-7, IL-8, IL-10 and IL-18[35,36].

A correlation has been shown between Th17 cells, a proinflammatory subset of CD4<sup>+</sup> T cells, and their affiliated cytokines (IL-17A, IL-17F, IL-21, IL-22 and IL-26) in persistent *H. pylori*-mediated gastric inflammation and the subsequent gastric cancer development[36,37]. We have demonstrated in a previous study that an IL-17 T-cell response predominates in *H. pylori*-associated gastritis in adults, whereas, in children, there is predominance of a T regulatory (Treg) cell response. IL-17A is known to play an important role in the recruitment and activation of polymorphonuclear cells that are vital for *H. pylori* clearance. Treg and Th17 cells are mutually controlled. Therefore, these findings could explain the higher susceptibility of children to the infection and bacterial persistence[38].

IL-27 expression differs between *H. pylori*-related diseases. Accordingly, we have shown that there is a high expression of IL-27 in the gastric mucosa and serum of *H. pylori*-positive duodenal ulcer patients. In contrast, IL-27 is absent in the gastric mucosa and serum of patients with gastric cancer. Consistent with the immunosuppressive role of IL-27 in Th17 cells and IL-6 expression, we observed that expression of Th17-cell-associated cytokines was lower in the patients with duodenal ulcer, which secreted a large concentration of proinflammatory Th1 representative cytokines. We demonstrated that there is high levels of IL-1 $\beta$ , IL-6, IL-17A, IL-23, and transforming growth factor- $\beta$ , involved in IL-17A expression, on the gastric mucosa and in the serum of gastric cancer patients. Therefore, IL-27 may be involved in the development of different patterns of *H. pylori*-induced gastritis and its progression. Taking into account that IL-27 has evident antitumor activity, our results point to a possible therapeutic use of IL-27 as an anticancer agent[39].

Recently, the role of the interaction between *H. pylori* infection and the gastrointestinal microbiome in gastric carcinogenesis has also been investigated. In this regard, researchers explored the diversity and composition of the gastric microbiome at different stages of disease, including normal gastric mucosa, chronic gastritis, atrophic gastritis, intestinal metaplasia, and gastric cancer[40]. A recent meta-analysis indicated that *H. pylori*-positive gastric samples exhibit reduced microbial diversity, altered microbial community, composition, and bacterial interactions. An increased abundance of opportunistic pathogens (*e.g.*, *Veillonella* and *Parvimonas*) was observed concomitantly with a decrease in putative probiotics (*e.g.*, *Bifidobacterium*) throughout the stages of disease progression[41]. Another study has suggested that successful eradication of *H. pylori* could reverse the tendency towards gastric microbiota

dysbiosis and show beneficial effects on the gastric microbiota[42]. The next step in this field could be to conduct a prospective, multicenter, crosscultural study to validate these results and explore the mechanisms underlying the *H. pylori*-gastric microbiota interaction and its role in gastric cancer development[43].

## CAGA — *H. PYLORI* TRANSLOCATED ONCOPROTEIN

CagA is a translocated effector protein that induces morphofunctional modifications in gastric epithelial cells and inflammatory responses, whose balance allows successful colonization of the acidic stomach environment[44,45]. The CagA gene is located in the *cagPAI*; a 40-kb DNA fragment that contains about 31 genes and confers virulence to some strains of *H. pylori*. Some genes of the island encode proteins that form a T4SS, which is responsible for the translocation of CagA into the cytoplasm of gastric epithelial cells through interaction of bacterial and host cell components[46-48]. The oncoprotein has a molecular weight of 128-145 kDa and its tertiary structure is characterized by a structured N-terminal region, split into Domains I-III and an unstructured C-terminal tail[49].

Injection of CagA depends on the recognition of its N-terminal and C-terminal portions by T4SS, which can occur simultaneously or not[50]. However, several other mechanisms are also required for its inoculation. We highlight the binding between T4SS CagL and CagY to human  $\beta$ 1-integrins[51,52], along with the CEACAMs and *H. pylori* outer membrane protein Q (HopQ) interaction, that allow the translocation of CagA into the host cells[53]. A recent study noted that the instability of the relationship between *H. pylori* HopQ and mouse CEACAMs may explain why the pathogenesis of infection in the stomach of rodents infected with CagA positive *H. pylori* strains occurs differently from infection by the same strain in humans. The authors also demonstrated that the presence of functional T4SS is associated with a time-dependent reduction in human CEACAM1 levels after CagA-positive *H. pylori* infection [54]. However, it is still unclear whether the instability of the HopQ-CEACAMs relationship favors the host or the bacterium, so more studies are needed to investigate the possibility of these interactions being beneficial in favor of the patient infected with *H. pylori*. BabA is apparently also capable of increasing T4SS activity[55].

CagA is known to possess multiple phosphorylation segments in its tertiary structure. The phosphorylation sites are denominated EPIYA sequences; regions consisting of five amino acids (Glu-Pro-Ile-Tyr-Ala) located in the C-terminal portion of the oncoprotein. Four different EPIYA segments have been described according to the different amino acid sequences surrounding each motif, designated EPIYA-A (32 amino acids), B (40 amino acids), C (34 amino acids) and D (42 amino acids). EPIYA-A and EPIYA-B motifs have been identified in almost all CagA-positive *H. pylori* strains, followed by one, two, or three EPIYA-C sequences in western strains, or an EPIYA-D segment in East Asian strains[56,57]. Figure 1A summarizes the main structural domain differences between East Asian and western CagA.

Once inside the gastric epithelial cells, the EPIYA segments are selectively tyrosine-phosphorylated by different kinases of the Src family (s-Src, Fyn, Lyn and Yes) or by Abl kinase of the host cells[58-61]. After the phosphorylation process, CagA moves to the cell membrane and acts as a promiscuous scaffold protein that simultaneously disturbs multiple signaling pathways, involved in the regulation of a large range of cellular processes, including proliferation, differentiation and apoptosis[62].

In this sense, a better understanding of the molecular structure of CagA and the interactions promoted by CagA-positive *H. pylori* strains to prevail in the host organism may be essential in identifying variations in prognosis, disease severity, and mechanisms that may be beneficial to the host, according to infections by different *H. pylori* strains.

## ROLE OF CAGA IN GASTRIC CARCINOGENESIS

The translocated effector protein CagA was found to be associated with gastric cancer development even before the initial elucidation of its pathogenic mechanisms[63,64]. Initially, the correlation between infection with CagA-positive *H. pylori* strains and carcinogenesis *in vivo* was established by experiments in Mongolian gerbil models[65-67]. More recently, transgenic expression of CagA in mice and zebrafish has also been shown to be associated with the development of gastric and hematopoietic neoplasms[68, 69]. Thereby, the oncogenic potential of the bacterial protein has become increasingly evident and, at the same time, different studies have sought to clarify its underlying mechanisms. Nowadays, CagA is considered a pathological analog of a scaffold or hub protein capable of disrupting multiple host signaling pathways and promoting a pro-oncogenic microenvironment[70].

Upon translocation, CagA localizes to the inner surface of the plasmatic membrane, where it undergoes tyrosine phosphorylation by multiple members of the Src family kinases and c-Abl kinases[8, 10,59,61]. As mentioned above, four different EPIYA segments were described according to the different amino acid sequences surrounding each motif, designated EPIYA-A-EPIYA-D[56,57]. Strains containing EPIYA-D or at least two EPIYA-C motifs are known to be associated with an increased risk of

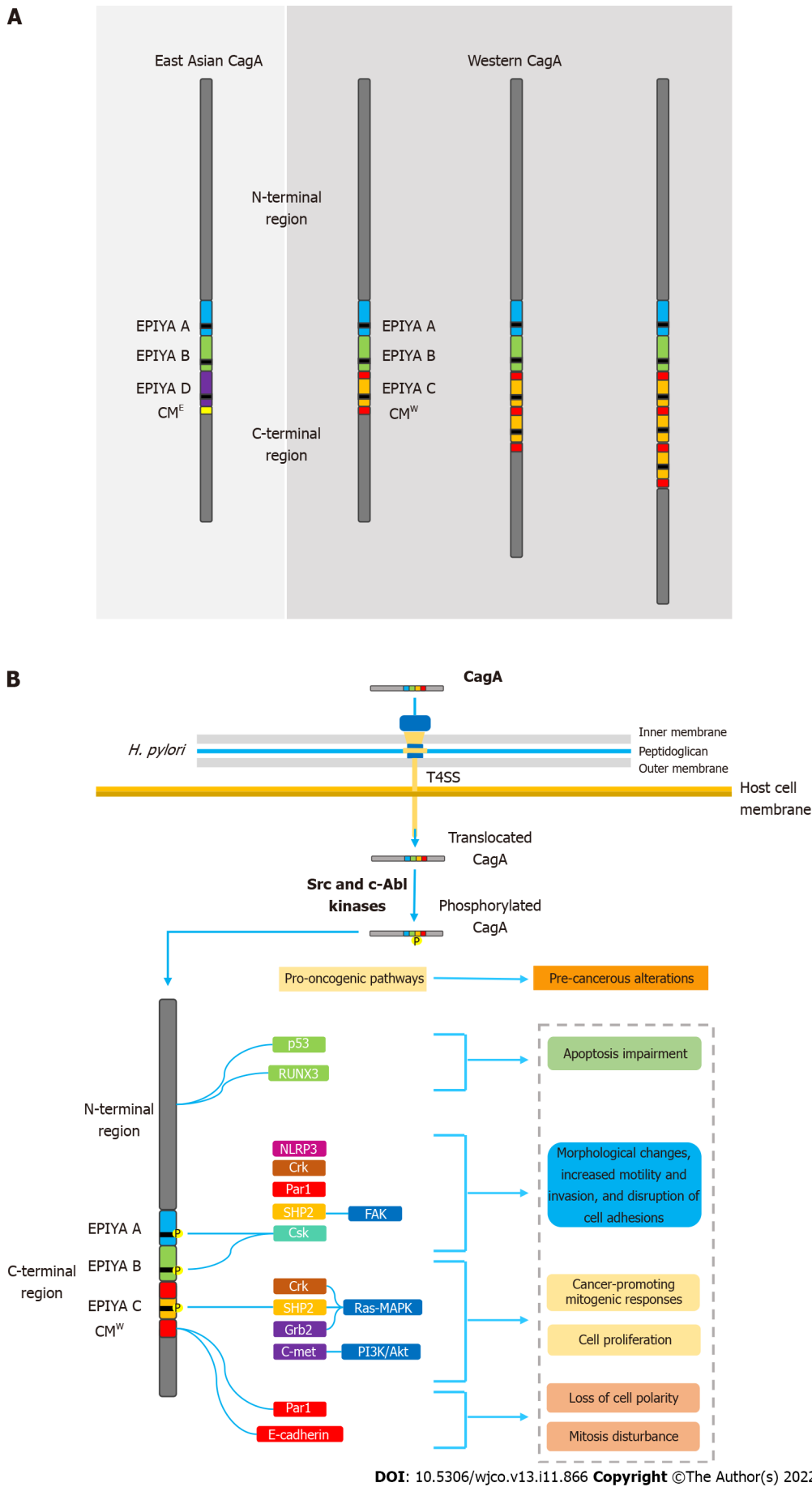


Figure 1 *Helicobacter pylori* oncoprotein: molecular structure and CagA-mediated carcinogenesis underlying mechanisms. A: Structural

domain differences between East Asian and western CagA. CagA tertiary structure is characterized by a structured N-terminal region and an unstructured C-terminal tail. The oncoprotein contains repetitive sequences in its C-terminal polymorphic region, known as the EPIYA motifs and CM motif. EPIYA-A and EPIYA-B motifs were identified in almost all CagA-positive *H. pylori* strains, followed by one, two, or three EPIYA-C sequences in western strains, or an EPIYA-D segment in East Asian strains. The CM motif, although highly conserved, possesses a 5-amino-acid difference between East Asian and western strains, hence distinguishing East Asian and Western CagA; B: Molecular mechanisms of CagA-mediated carcinogenesis. Upon translocation, CagA EPIYA motifs are tyrosine-phosphorylated by Src family or c-Abl kinases of the host cell. After phosphorylation, CagA localizes to the inner leaflet of the plasmatic membrane and acts as a promiscuous scaffold or hub protein that simultaneously disturbs multiple host signaling pathways, involved in regulation of a large range of cellular processes, including proliferation, differentiation and apoptosis. Ultimately, the disharmonic interaction between CagA and host proteins leads to pro-oncogenic cellular alterations. CM: CagA-multimerization; CM<sup>W</sup>: western CagA.

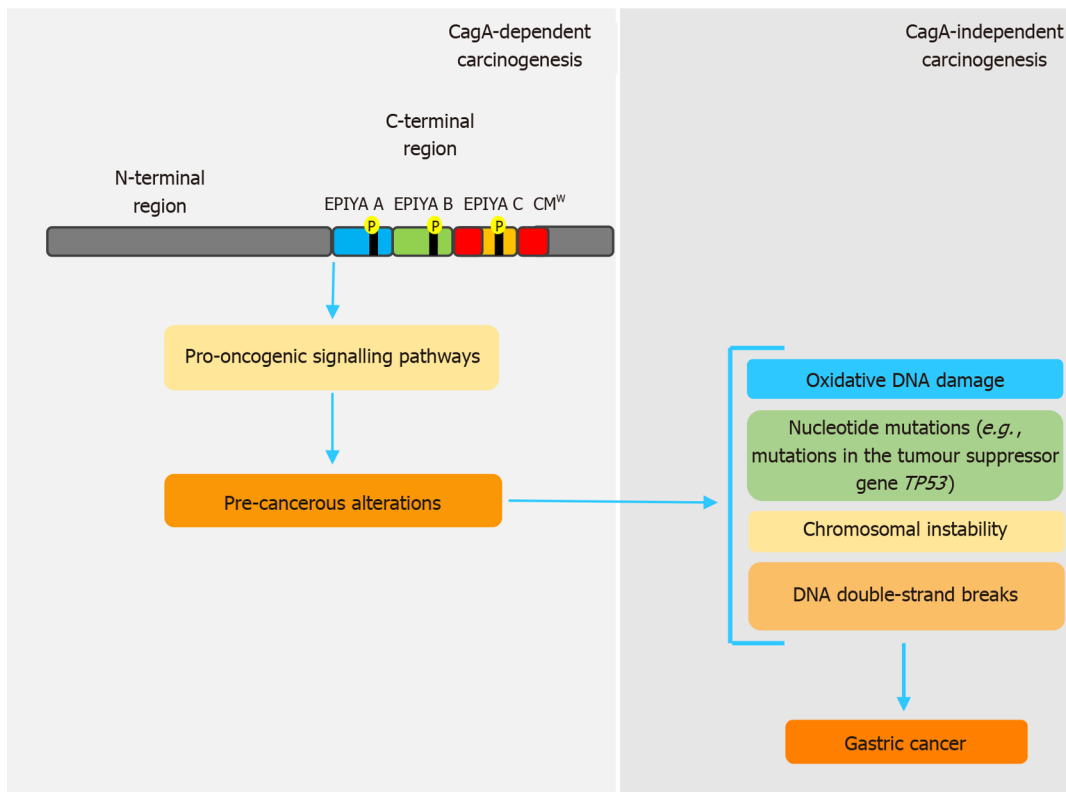
developing precancerous lesions and gastric cancer[71-75]. Queiroz *et al*[75] demonstrated in a Brazilian population that first-degree relatives of patients with gastric cancer were significantly and independently more frequently colonized by *H. pylori* strains with higher numbers of CagA EPIYA-C segments, which may be associated with an enhanced risk of developing this neoplasm[76].

Following tyrosine phosphorylation, EPIYA-C and D motifs acquire the ability to interact with SHP2 and induce pathological intracellular signaling[9]. Abnormal SHP2 activity leads to aberrant activation of the Ras-MAPK pathway, which has been associated with accelerated cell cycle progression and enhanced cell proliferation. CagA-activated SHP2 is also able to interact with proteins such as focal adhesion kinase, thence leading to cell elongation, increased motility, and cytoskeleton rearrangements [77,78]. All these pathological alterations in cell biology increase the risk of damaged cells acquiring precancerous genetic changes[79]. It is worth mentioning that CagA possessing EPIYA-D or a higher number of EPIYA-C segments binds more robustly to SHP2, which may explain their association with higher risk of gastric cancer development[8]. It has also been described that EPIYA-A and B motifs are able to interact with the SH2 domains of the tyrosine-protein kinase Csk, thereby inducing damage to actin binding proteins such as cortactin and vinculin. Consequently, rearrangements in the cytoskeleton reduce cell adhesion to the extracellular matrix and increase cell motility[80]. A recent study observed that *H. pylori*, through the T4SS encoded by *cagPAI*, interferes with the activity of cortectin binding partners, and stimulates overexpression of this molecule and promotes alterations in the actin cytoskeleton that may favor cell adhesion, motility and invasion of tumor cells contributing to the development of gastric cancer[81].

Recent studies have described that SHIP2, an SH2-containing phosphatidylinositol 5'-phosphatase, is a previously undiscovered CagA binding protein. Similar to SHP2, the SHIP2 protein is able to bind to EPIYA-C and D motifs in a tyrosine phosphorylation-dependent manner. In contrast, SHIP2 binds more robustly to EPIYA-C than to EPIYA-D sequences, thereby inducing changes in membrane phosphatidylinositol composition. This process enhances the subsequent delivery of CagA to the host cell, which binds to and dysregulates SHP2[82].

Other mechanisms have also been related to the aberrant induction of morphological changes, increased motility and cell proliferation[83]. In a tyrosine-phosphorylation-dependent manner, the interaction of CagA with the adapter molecule Crk is known to drive abnormal cell proliferation *via* MAPK signaling. Furthermore, the activation of Crk signaling pathways lead to the loss of cell-cell adhesion, hence inducing cell scattering/hummingbird phenotype and cell-cell dissociation[84]. It is important to mention that the EPIYA motif that corresponds to the binding site Csk has not been identified yet. In contrast, activation of the growth factor receptor-bound protein 2 (Grb2) protein and the *C-Met* oncogene in a tyrosine-phosphorylation-independent manner can also lead to similar pathological effects, highlighting the multiplicity of pro-oncogenic mechanisms of CagA[85,86]. Grb2 is an important regulator of Ras-MAPK pathway activation, capable of deregulating cell proliferation. Activation of C-Met-mediated PI3K/Akt signaling is associated with cancer-promoting mitogenic and inflammatory response[87-91].

The ability of CagA to disrupt the epithelial barrier has also been widely linked to its carcinogenic potential. In addition to the EPIYA sequences, the oncoprotein contains another repetitive sequence in its C-terminal polymorphic region, known as the CagA-multimerization (CM) motif[90]. With its number varying between different strains, the CM motif is composed of a 16-amino-acid sequence located downstream of the last EPIYA sequence[89]. This sequence, although highly conserved, possesses a 5-amino-acid difference between East Asian and western strains, hence distinguishing East Asian and western CagA (CM<sup>W</sup>)[91]. Thus, higher number of EPIYA-C motifs also increases the number of CM motifs in the CM<sup>W</sup>. The CM motif is identified as the main mediator of the interaction between CagA and the partitioning-defective 1 (PAR1)/microtubule affinity-regulating kinase, which plays a pivotal role in establishing epithelial polarity. As a result, there is loss of cell polarity, as well as induction of morphological alterations also associated with the hummingbird phenotype[92]. CagA-mediated PAR1 inhibition also disrupts mitosis, causing increased cell division and impaired segregation of sister chromatids, thus leading to chromosomal instability (CI)[93]. Currently, CI is widely recognized for its multifactorial role in carcinogenesis and its microenvironment[94].



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**Figure 2 Simplified model of CagA-mediated hit-and-run carcinogenesis.** The pro-oncogenic properties of CagA are already well established. However, genetic and epigenetic alterations caused by this oncoprotein provide a favorable environment for carcinogenesis, independently of its presence, in a hit-and-run carcinogenesis mechanism. In this sense, through interaction with various host proteins, CagA leads to chromosomal instability, double-strand breaks and repeated nucleotide mutations, which are correlated to gastric cancer development. CM<sup>W</sup>: western CagA.

From a different perspective, there is also a dangerous association between CM motifs and E-cadherin, a key protein in establishing cell polarity and maintaining epithelial integrity and differentiation[95-97]. It has been described that the CagA-E-cadherin interaction downregulates the  $\beta$ -catenin signal that promotes intestinal transdifferentiation in gastric epithelial cells. Therefore, it was inferred that the oncoprotein plays an important role in the development of intestinal metaplasia, a precancerous transdifferentiation of gastric epithelial cells from which intestinal-type gastric adenocarcinoma emerges [98].

Also in this sense, a recent study observed that CagA seems to be able to induce gastric carcinogenesis by stimulating the migration of cancer cells through the activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome. The authors reported that CagA also participates in the generation of intracellular ROS and that ROS inhibition has the potential to disrupt the NLRP3 pathway and pyroptosis. With these findings, the authors concluded that NLRP3 plays a key role in the action of CagA on gastric cells and that silencing NLRP3 can limit the effects of migration and invasion of cancer cells caused by CagA[99].

It is worth emphasizing the ability of CagA to activate a variety of antiapoptotic pathways, upon interaction of its N-terminal portion with various tumor suppressor factors. For example, it is well described that CagA is able to impair the antiapoptotic activity of the tumor suppressor factor p53. CagA protein induces degradation of p53 protein in both ASPP2- and p14ARF-dependent manners[100, 101]. Furthermore, it is known that the interaction of the oncoprotein with Runt-related transcription factor 3 (RUNX3) is able to induce the ubiquitination and degradation of RUNX3 that blocks its antitumoral activity[102]. Figure 1B summarizes the main molecular mechanisms of CagA-mediated carcinogenesis.

Another important potential of CagA associated with gastric cancer pathogenesis is the ability to drive epithelial to mesenchymal transition (EMT); a phenomenon extensively related to carcinogenesis [103,104]. EMT is the result of a complex molecular program that allows cancer cells to suppress their epithelial characteristics, transforming themselves into mesenchymal epithelial cells. This change allows the cells to acquire motility, invasiveness, greater resistance to apoptosis, and the ability to migrate from the primary site[104,105]. In this regard, it has been shown that EMT gene expression is upregulated in gastric epithelial cells infected with *H. pylori* CagA-positive strains[106]. Nevertheless, multiple pathogenic mechanisms have been described, including reduction of glycogen synthase kinase-3 activity and triggering of the YAP oncogenic pathway, for example. However, the multiplicity of processes

involved in EMT and its role in gastric cancer development still requires further explanation[107,108].

Recent studies have not been limited to pathogen–host interactions in *H. pylori* infection, but have also investigated the mechanisms regulating bacterial virulence factors, such as CagA, and their relation to carcinogenesis. Eisenbart *et al*[11] identified a conserved, abundant nickel-regulated sRNA and named it NikS (nickel-regulated sRNA), whose expression is transcriptionally modulated based on the size of a variable thymine stretch in its promoter region. NikS, in dependence on nickel availability, directly represses several virulence factors of *H. pylori*, including the oncoprotein, CagA, and its effects on host cell internalization and epithelial barrier disruption. In this sense, multiple clinical repercussions of post-transcriptional modulation of CagA by NikS can be hypothesized, including decreased activation of procarcinogenic signaling. Kinoshita-Daitoku *et al*[109] described that NikS expression is lower in clinical isolates from gastric cancer patients than in isolates from noncancer patients, while the expression of virulence factors targeted by NikS, including CagA, is increased in isolates from gastric cancer patients. This field needs to be better explored, especially regarding the correlation of NikS with the multiple virulence factors of *H. pylori* and its potential clinical repercussions.

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## CAGA-MEDIATED HIT-AND-RUN CARCINOGENESIS

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Even though CagA is notably a pro-oncogenic virulence factor, once gastric cancer sets in, its perpetuation is independent of the presence of this oncoprotein. In this sense, genetic and epigenetic changes caused by CagA seem to be responsible for this process, in a mechanism called “hit-and-run” carcinogenesis[58,92], firstly proposed by Skinner[110] for virus-induced cancers. Apparently, these changes are intrinsically related to disorders in the expression of activation-induced cytidine deaminase (AID), a crucial enzyme in the processes of somatic hypermutation and class-switch recombination of immunoglobulin genes in B cells[111,112]. Matsumoto *et al*[111] state that *cagA*-positive *H. pylori* induces disordered expression of AID via NF- $\kappa$ B, which consequently leads to various nucleotide mutations, such as in the tumor suppressor gene *TP53*. *cagA*-positive *H. pylori* strains are also related to oxidative DNA damage, because they are able to promote increased levels of H<sub>2</sub>O<sub>2</sub> and downregulation of heme oxygenase-1[89,113]. CagA also inhibits PAR1 kinase, leading to microtubule-based spindle dysfunction and consequent CI[93].

Some studies have shown that *H. pylori* can also promote DNA double-strand breaks (DSBs) in host cells[114,115], but whether or not this feature is CagA-related remains uncertain. However, a recent study showed that inhibition of PAR1b kinase by CagA hindered *BRCA1* gene phosphorylation, which leads to a BRCAness picture that, in turn, induces DSBs[116]. All these genetic and epigenetic changes support the hit-and-run mechanism, in which, regardless of the presence of CagA, the established pro-oncogenic environment maintains the acquired phenotype. Figure 2 summarizes the main features regarding CagA-mediated hit and run carcinogenesis mechanism.

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## CONCLUSION

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In this study, we address the role of CagA in the development of *H. pylori*-mediated gastric carcinogenesis and discuss the perspectives in this field of study (Figure 3). CagA undergoes important translocation and tyrosine phosphorylation before disrupting several cell signaling pathways and promoting protein dysfunction. However, there is still much to be clarified regarding the steps involved in the role of CagA in gastric carcinogenesis. Recent discoveries such as the identification of the SHIP2 binding protein capable of binding to the EPIYA-C and D motifs and potentiating the delivery of CagA to infected cells, or discovery of the instability between the *H. pylori* HopQ and CEACAM relationship, are significant findings that can generate advances in the area, and therefore, need to be investigated in more depth. Exploration of the little-known field of regulatory RNAs seems promising for a broader understanding of the control mechanisms involved in *H. pylori* infection and CagA levels and has the potential to identify factors with important clinical repercussions for conditions such as gastric cancer. Finally, the ability of *H. pylori* to evolve as a pathogenic bacterium and as a carcinogen is undeniable, therefore, it is essential to clarify what is still unclear about the subject and periodically monitor the behavior of the bacterium in the infection, the molecular processes and elements such as CagA to advance the diagnosis and treatment of the disease.



CagA-related pathogenic mechanisms	
Well-established mechanisms	Mechanisms under investigation
CagA-mediated SHP2 triggering, which leads to abnormal cell proliferation, motility and morphological changes	The relationship between <i>H. pylori</i> /HopQ and CEACAMs - differences in animal models and humans
CagA-Csk-associated reduction of cell adhesion to the extracellular matrix and increased cell motility	CagA strains with higher numbers of EPIYA-C segments and increased risk of gastric cancer
CagA-Crk interaction, inducing abnormal cell proliferation and hummingbird phenotype	SHIP2 binding protein and EPIYA-C and D motifs
Grb2-mediated pro-mitogenic responses	Crk binding site
CagA-PAR1 interaction causing morphofunctional alteration and loss of cell polarity	EMT underlying mechanisms and gastric cancer development
E-cadherin dysregulation-associated gastric cell transdifferentiation	Clinical repercussions of CagA post-transcriptional modulation by NikS
RUNX3 degradation and the blockade of antitumour activity	CagA-PAR1 mediated chromosomal instability
ASSP2-mediated p53 inactivation and degradation	CagA-mediated DNA double strand break, oxidative DNA damage and nucleotide mutations

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**Figure 3 Status of the current understanding regarding CagA-related pathogenic mechanisms.** EMT: Epithelial to mesenchymal transition; CEACAMs: Carcinoembryonic antigen-related cell adhesion molecules; Grb2: Growth factor receptor-bound protein 2; ASPP2: Apoptosis-stimulating protein of p53 2; SHP2: Domain-containing protein tyrosine phosphatase 2; SHIP2: Src homology 2 domain-containing inositol 5'-phosphatase 2; RUNX3: Runt-related transcription factor 3; PAR1: Partitioning-defective 1; NikS: Nickel-regulated sRNA.

## FOOTNOTES

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**Country/Territory of origin:** Brazil

**ORCID number:** Fabrício Freire de Melo 0000-0002-5680-2753; Hanna Santos Marques 0000-0001-5741-1570; Samuel Luca Rocha Pinheiro 0000-0002-8877-892X; Fabian Fellipe Bueno Lemos 0000-0002-4686-7086; Marcel Silva Luz 0000-0003-1650-5807; Cláudio Lima Souza 0000-0002-8094-8357; Márcio Vasconcelos Oliveira 0000-0002-8959-0478.

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