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Priming the seed: *Helicobacter pylori* alters epithelial cell invasiveness in early gastric carcinogenesis

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Abstract

Helicobacter pylori (*H. pylori*) infection is a well-established risk factor for the development of gastric cancer (GC), one of the most common and deadliest neoplasms worldwide. *H. pylori* infection induces chronic inflammation in the gastric mucosa that, in the absence of treatment, may progress through a series of steps to GC. GC is only one of several clinical outcomes associated with this bacterial infection, which may be at least partially attributed to the high genetic variability of *H. pylori*. The biological mechanisms underlying how and under what circumstances *H. pylori* alters normal physiological processes remain enigmatic. A key aspect of carcinogenesis is the acquisition of traits that equip preneoplastic cells with the ability to invade. Accumulating evidence implicates *H. pylori* in the manipulation of cellular and molecular programs that are crucial for conferring cells with invasive capabilities. We present here an overview of the main findings about the involvement of *H. pylori* in the acquisition of cell invasive behavior, specifically focusing on the epithelial-to-mesenchymal transition, changes in cell polarity, and deregulation of molecules that control extracellular matrix remodeling.

Key words: *Helicobacter pylori*; Plasminogen activation system; Invasion; Epithelial-to-mesenchymal transition;

Cell polarity; Gastric carcinogenesis

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Core tip: *Helicobacter pylori* (*H. pylori*) infection induces chronic inflammation in the gastric mucosa that, in the absence of treatment, may progress through a series of steps to gastric cancer (GC). GC is only one of several clinical outcomes associated with this bacterial infection, which may be at least partially attributed to the high genetic variability of *H. pylori*. Accumulating evidence implicates *H. pylori* in the manipulation of cellular and molecular programs that are crucial for conferring the cells with invasive capabilities, including reprogramming of the epithelial-to-mesenchymal transition signaling programs, changing of the cell apicobasal polarity, and remodeling of the extracellular matrix.

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INTRODUCTION

Persistent *Helicobacter pylori* (*H. pylori*) infection induces chronic inflammation in the gastric mucosa, which in susceptible individuals may progress to gastric cancer (GC)^[1,2]. The final clinical outcome of the infection depends on complex interactions among the infecting strain of the bacterium, the host, and the environment^[3]. The biological mechanisms underlying how and under what circumstances *H. pylori* alters normal physiological processes in such a way that sequential events culminate in the development of GC remain largely unknown.

A key feature of malignant transformation and progression is the invasion of malignant cells locally and then to distant sites (metastasis)^[4]. Invasion and metastasis occur through a series of events in which several processes take place, including reprogramming of signaling pathways that drive the epithelial-derived malignant cells into a mesenchymal-like phenotype, the so-called epithelial-to-mesenchymal transition (EMT), changing of the cell polarity, and remodeling of the extracellular matrix (ECM)^[5,6]. Several of these events are activated in gastric epithelial cells by *H. pylori* directly or as a result of the inflammatory reaction mounted in response to this bacterial infection. This review summarizes the current evidence implicating *H. pylori* in the activation of molecular and cellular mechanisms related to invasion in the early stages of the pathogenic series of events leading to GC. Specifically, we address the role of *H. pylori* in the deregulation of molecules that control EMT, cell polarity, and ECM remodeling.

EPIDEMIOLOGY

GC is the fifth most common and the third death-causing cancer worldwide^[7]. Incidence rates vary considerably depending on age and sex; however, the most substantial variation is connected to geographic location, with very well-established high- and low-risk areas across the world^[8,9]. GC incidence is steadily declining worldwide; and although the reasons are not clear, this may be at least partially linked to the concomitant decrease in *H. pylori* prevalence^[8]. The decrease, however, is not of the same magnitude in GC of different histological subtype or anatomical location^[10]. Similarly, mortality rate varies geographically, being particularly high in developing countries but declining globally^[8,9]. The 5-year survival rate remains below 30% in most countries, which is mainly connected to the fact that most of the cases are diagnosed at advanced stages, when therapeutic interventions are likely to fail.

HISTOPATHOLOGY

Several schemes are used for classifying GC according to microscopic and histological characteristics. The Lauren classification system is probably the most commonly used^[11,12]. The Lauren system divides GC into intestinal, diffuse and mixed subtypes, with important differences at the epidemiological, pathological and molecular levels^[11,13].

Marked epidemiological and etiological differences have been revealed for malignant tumors located in the distal part of the stomach and those of the proximal region^[14,15]. Therefore, anatomical location of the lesions is regarded as an important parameter in the classification of GC.

PATHOGENESIS

The pathogenesis of GC is a complex and multifactorial process in which environment and lifestyle, host genetics, and *H. pylori* infection play a role^[2,16-21]. As already mentioned, the pathogenesis of GC substantially differs depending on the histological and anatomical subtype. The intestinal subtype of GC, for instance, arises through a sequential series of steps known as the Correa cascade^[22], in which *H. pylori* plays a pivotal role. The infection is usually established early in life and persists lifelong in the absence of treatment, which in combination with environmental factors leads to sustained chronic inflammation characterized by infiltration of inflammatory cells in the gastric mucosa and expression of inflammatory mediators.

Intriguingly, most of the infected individuals remain asymptomatic, while others develop pathologies that are not related to GC. In a minority of infected people, the inflammation evolves into a chronic atrophic gastritis, which is regarded as a pre-neoplastic lesion^[22,23]. This may subsequently progress to intestinal metaplasia, dysplasia, and invasive carcinoma^[22]. Much less is known

about the pathogenesis of the diffuse subtype of GC^[24,25] and the malignant lesions arising in the most proximal segment of the stomach^[26].

H. PYLORI

Infection with *H. pylori* is one of the most prevalent bacterial infections worldwide^[27]. This bacterium utilizes several strategies for colonizing and surviving in the hostile environment of the stomach. Some of these are common bacterial mechanisms of acid resistance, such as proton pump activation, decarboxylases, and membrane lipid modification^[28]. More specific adaptations to the acidic environment include the enzyme urease, which is encoded by the *ure* gene cluster and catalyzes the conversion of urea into ammonium and carbon dioxide. Urease was, in fact, the first protein identified in *H. pylori* with a role in neutralizing gastric acid, and it is considered a virulence factor^[29] since it has proven essential to the survival of the bacterium in the gastric mucosa^[30,31]. Besides the *ure* gene cluster, transcriptional regulation in response to acid extends to other genes related to motility, chemotaxis, and virulence^[32].

The genetic variability of *H. pylori* is high, and it probably explains in part the association of this infection with several gastric and extra-gastric pathologies, in addition to GC. Some strains, however, are more strongly associated with GC, namely those harboring particular polymorphic variants in the gene encoding the vacuolating cytotoxin A (VacA) and the ones expressing the Cag pathogenicity island (Cag-PAI)^[3,33-36]. Despite no physical or functional relation known for *vacA* and *cag-PAI* loci, strains that express virulent VacA usually contain functional Cag-PAI^[35,37]. In addition to VacA and Cag-PAI, other virulence factors of *H. pylori* have been associated with gastric pathology, including BabA, SabA, OipA, and DupA (Figure 1)^[3,36].

INVASION AND METASTASIS

The dissemination of cancer cells from primary lesions to form new tumor colonies at distant sites is a key feature of cancer^[4]. This occurs in a multistep process, termed the invasion-metastasis cascade: cancer cells locally invade, intravasate into the vascular system, travel in the circulation, extravasate at distant sites, form micrometastatic nodules of cancer cells, and, finally, grow into overt metastatic lesions^[5,6]. Importantly, early in this series of events, malignant cells acquire traits that equip them with the ability to invade, leave, and travel to distant tissues. A centrally important process that confers epithelial-derived malignant cells with increased motility and invasiveness is the EMT program^[38,39].

In order to become invasive, cells commonly lose their apico-basal polarity due to rearrangements in the cytoskeleton, which maintains the shape and internal organization of the cells, and modifications in the intercellular unions that hold them together^[39,40]. Also, the degradation of ECM components is essential

in several phases of the invasion-metastasis cascade. ECM remodeling is primarily mediated by proteases that belong to the plasminogen activation (PA) system and the matrix metalloproteinase (MMP) family^[41,42]. The cellular and molecular mechanisms underlying these processes, as well as their regulation, have been reviewed in depth^[39,40,43-45]. Accumulating experimental evidence has implicated *H. pylori* in all these aspects (Figure 2), as discussed below.

EMT and *H. pylori*

EMT is an evolutionary conserved, reversible process in which polarized epithelial cells acquire a mesenchymal phenotype through phenotypical and biochemical changes, thereby resulting in increased capacities of migration, invasion, and apoptosis resistance as well as ECM production and remodeling^[38]. Transcription factors such as Snail, Slug, zinc-finger E-box binding (ZEB1/2) and FOXC2 are activated at the beginning of the process. This is accompanied by the expression of specific microRNAs (miRs), for instance the miR-200 family, changes in the expression of particular cell surface proteins, cytoskeletal reorganization, and activation of Wnt/ β -catenin and Notch signaling^[38,46,47].

A critical feature of EMT is the down-regulation of E-cadherin^[48], a surface glycoprotein expressed in epithelial cells that is a key component of the adherent junctions in epithelial tissues^[49]. Expression of E-cadherin can be repressed directly or indirectly by multiple transcription factors, including ZEB1/2, Snail, Slug, nuclear factor-kappa B (NF- κ B), E47 and KLF8, but also by the proteins SIX1 and FOXC2^[50-52]. Furthermore, various signaling pathways can influence the expression of E-cadherin, including TGF β , hypoxia-induced response, Wnt/ β -catenin, Notch and PI3K/Akt, and therefore play a role in EMT^[53,54]. Although EMT is usually depicted as a binary switch that shifts cells from a fully epithelial to a fully mesenchymal state, this is a misrepresentation of this process. Frequently, the EMT program drives cells from a fully epithelial state to a partially mesenchymal one in which some epithelial markers are retained. Nonetheless, this subset of mesenchymal traits has profound effects on the cell biology^[55].

Activation of EMT programs in neoplastic cells is usually connected to their dedifferentiation and acquisition of stem cell-like properties^[56]. The existence of cancer cells with stem-like properties, the so-called cancer stem cells (CSCs), was first described in breast cancer and subsequently documented in various malignancies, including GC. One of the first studies about CSCs in GC showed that these cells have enhanced capability of invasion and tumorsphere formation. Also, it was found that CSCs have distinctive features of the EMT, such as reduced expression of E-cadherin and increased levels of vimentin and MMP2^[57]. In primary GC tissue, it was demonstrated by immunohistochemistry that the combination of Snail-1, vimentin, E-cadherin and CD44 predicts tumor aggressiveness^[58]. Furthermore,

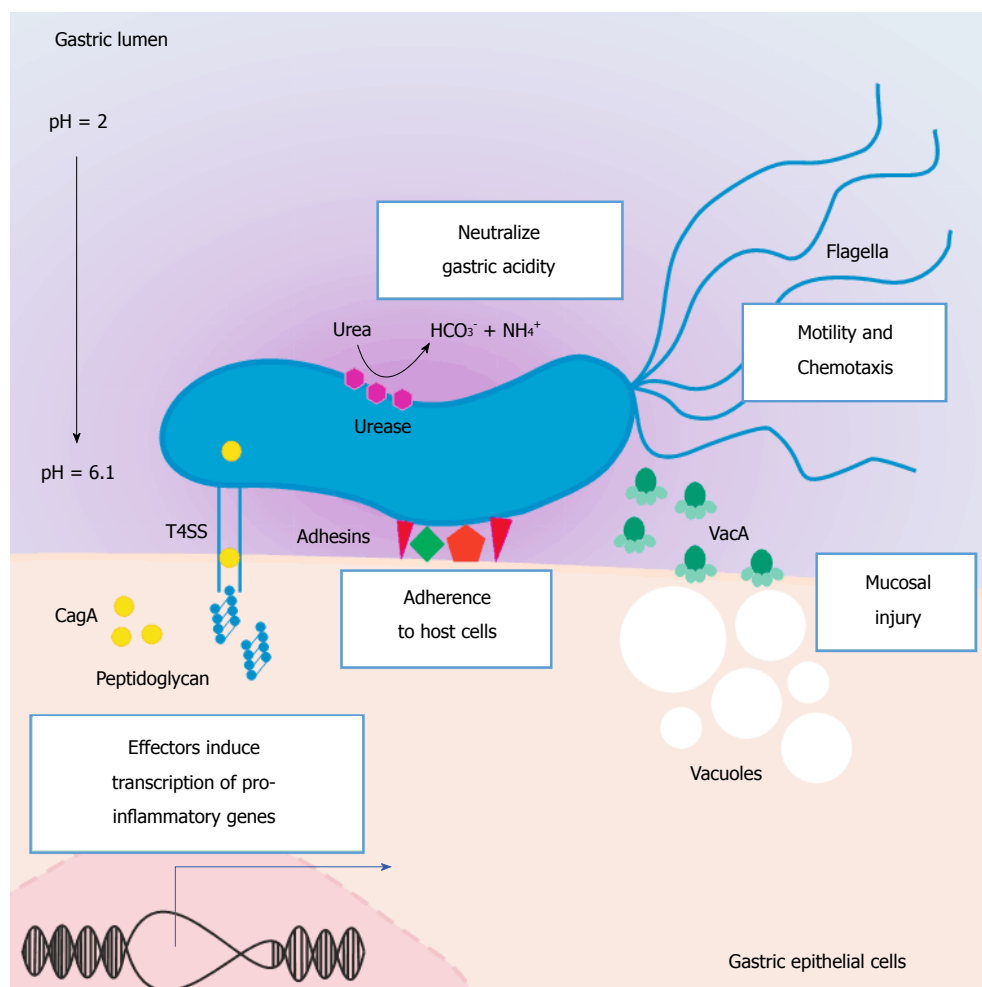


Figure 1 *Helicobacter pylori* virulence factors associated with gastric pathogenic processes. *H. pylori* is genetically highly variable, and some strains are more strongly associated with gastric pathologies, including GC. The most prominent are those that express the virulence factors VacA and Cag-PAI. VacA is a cytotoxic protein expressed by the polymorphic gene *vacA* that induces the formation of vacuoles, thus generating damage in the gastric epithelium. The Cag-PAI-positive strains (approximately 60%) possess a functional genetic region, which contains approximately 30 genes that code for proteins, that together make up a T4SS. The secretion system introduces a number of molecules, including the virulence factor CagA and peptidoglycans, into the cytoplasm of epithelial cells of the gastric mucosa. Once in the cytoplasm, CagA is phosphorylated, and this triggers downstream intracellular events, such as cytoskeletal rearrangement, alterations in cellular polarity, expression of inflammatory mediators, and activation of signaling pathways that promote cellular proliferation. The conversion of urea into ammonium and carbon dioxide by urease is essential to the survival *H. pylori* in the stomach. Flagella play an important role in the colonization of the gastric mucosa, as they produce differential motility depending on the pH of the stomach lumen and the concentration of compounds such as urea, thus enabling *H. pylori* bacteria to swim across the mucous layer towards the epithelial lining. Other less well-characterized virulence factors of *H. pylori* associated with gastric pathology are the adhesins, which include BabA, SabA, and OipA. Cag-PAI: Cag pathogenicity island; GC: Gastric cancer; *H. pylori*: *Helicobacter pylori*; T4SS: Type IV secretion system; VacA: Vacuolating cytotoxin A.

it has been reported that MKN7 GC cells undergoing Wnt5a-induced EMT acquire CSC properties^[59], similar to what has been observed in hypoxia-driven EMT *in vitro* models with the BGC823 and SGC7901 GC cell lines^[60].

Using *in vitro* systems, it was revealed that *H. pylori* infection results in the activation of EMT programs and the emergence of CD44^{high} cell populations with CSC properties in the AGS, MKN45 and MKN74 GC cell lines^[61]. These cells acquire elongated shape and show enhanced expression of mesenchymal markers (*i.e.*, Snail1, ZEB1, and vimentin). Compared to the CD44^{low} cells, the CD44^{high} GC cell population gained the ability to migrate and invade and was better at forming tumorspheres *in vitro* and tumors in immunodeficient mice. According to that study, the induction of the EMT

and CD44^{high} cell population was dependent on the CagA oncoprotein. CagA induces the EMT in a number of ways, as exemplified by a recent *in vitro* study showing that this bacterial protein up-regulates MMP3, which is also part of the EMT program, through EPIYA motifs in a phosphorylation-dependent manner^[62]. Immunohistochemistry staining of human and murine gastric tissue have confirmed that *H. pylori* infection is correlated with high expression of CD44 and EMT markers^[61]. Presumably, ERK and JNK are involved in the described EMT-like changes, CD44 overexpression and the ability to form tumorspheres *in vitro* that is triggered by *H. pylori* cagA-positive strains^[61].

Other studies addressing the potential induction of CSC-like properties by *H. pylori* concluded that Wnt/

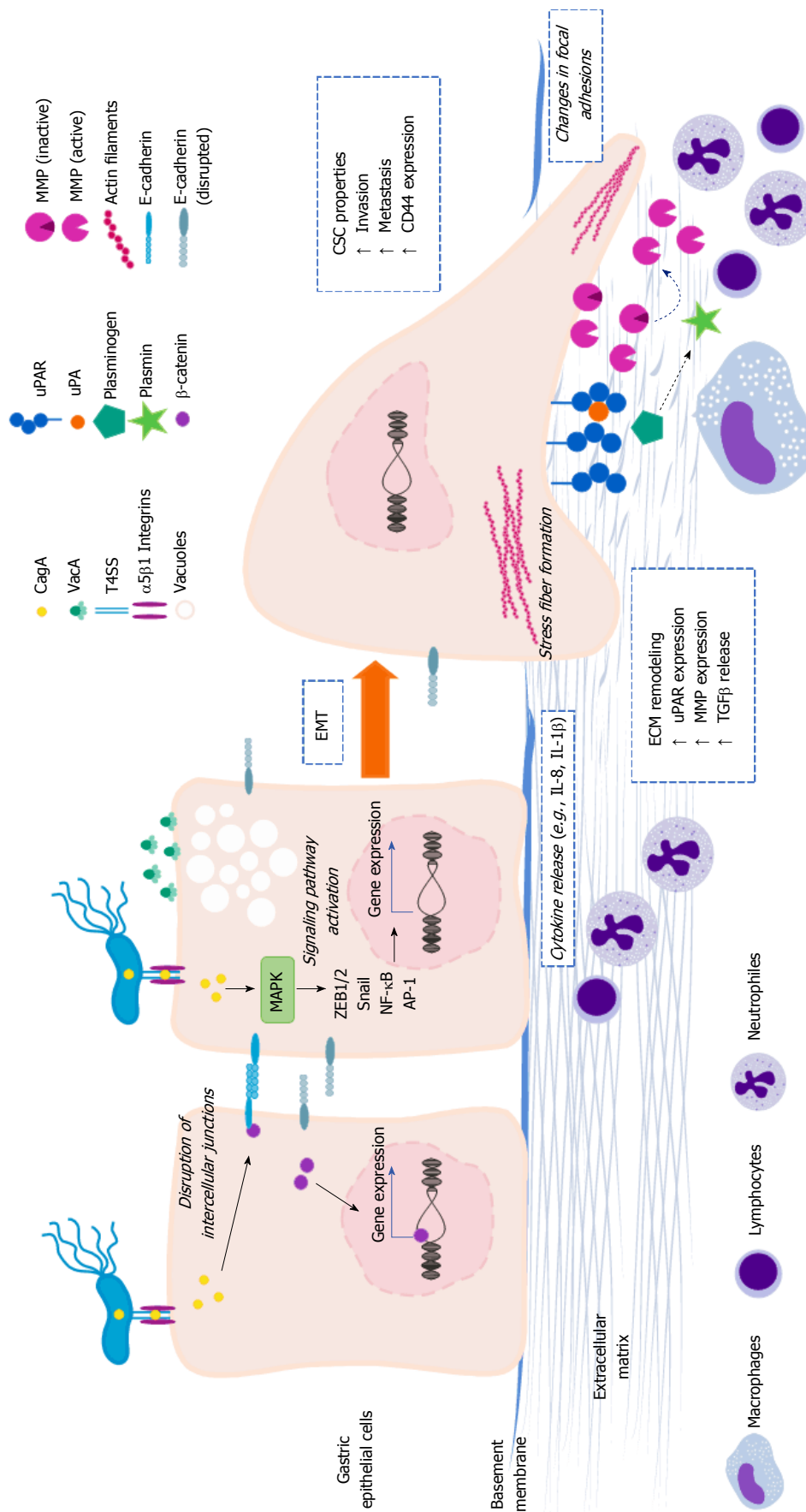


Figure 2 Role of *Helicobacter pylori* in the reprogramming of cellular and molecular programs related to invasive behavior. Upon infection, *H. pylori* induces a number of intracellular processes in gastric epithelial cells, some of them can result in the reprogramming of cellular and molecular mechanisms underlying the invasive cell behavior. Several of these events take place after phosphorylation of CagA, others may be independent of the translocation and phosphorylation of CagA, and a portion are not connected to the Cag-PAI at all. Although not exclusively, CagA plays an important role in the activation of transcription factors, such as β -catenin, Snail, ZEB1/2, NF- κ B, and AP-1. Some of these transcriptional regulators (e.g., β -catenin, Snail, ZEB1/2) modify the expression of genes encoding for key effectors of the EMT and stem cell programs, including up-regulation of TGF β and CD44 and down-regulation of E-cadherin. Changing of the gastric epithelial cell polarity is another downstream intracellular event connected to *H. pylori*, which is primarily attributed to the physical interaction of components of the T4SS (especially CagL) and $\beta 1$ integrins. In addition to this translocation-independent mechanism, alteration of the cell polarity can also result from CagA translocation and phosphorylation. Another consequence of the manipulation of the invasive properties by *H. pylori* is the induction of the expression of ECM remodeling effectors, namely uPAR, uPA, MMP7, MMP2, MMP3, and MMP9. This is presumably linked to the activation of the MAPK signaling pathway, which in turn leads to the activation of NF- κ B and AP-1. It is not yet clear whether plasminogen and MMP activation (dashed arrows) takes place, or what are the functional implications of the enhanced expression of these ECM-related molecules in this particular context. Cag-PAI: Cag pathogenicity island; ECM: Extracellular matrix; EMT: Epithelial-to-mesenchymal transition; *H. pylori*: *Helicobacter pylori*; MMP: Matrix metalloproteinase; NF- κ B: Nuclear factor-kappa B; T4SS: Type IV secretion system; uPA: Plasminogen activator; uPAR: Plasminogen activator receptor.

β -catenin activation in response to this bacterial infection is a necessary event for the acquisition of such properties in GC cell lines^[63]. Finally, observations on patients with gastric dysplasia and early GC, before and after eradication of *H. pylori*, showed a connection between the mRNA expression levels of TGF- β 1, EMT markers, and immunohistochemical expression of CD44, suggesting that *H. pylori* infection may trigger a TGF- β 1-induced EMT and the emergence of CSCs^[64].

Cell polarity alterations induced by *H. pylori*

Epithelial cells in the gastrointestinal tract are normally found in organized layers or epithelia. Their polygonal shape and functional organization in an apico-basal polarized manner allow them to lay in an orderly fashion, and the unions they form with each other and with the basal membrane give the epithelium a barrier function. As already mentioned, invasiveness is enhanced when cells lose their polarity due to alterations in the cytoskeleton and intercellular unions. *H. pylori* has been implicated in changing the polarity of the gastric epithelial cells, which may have important consequences in the context of gastric carcinogenesis. Of the three types of filaments that compose the cytoskeleton, the actin microfilaments are the most affected during *H. pylori* infection.

The actin cytoskeleton is a very dynamic structure whose assembly is finely tuned by complex signaling networks and involves numerous regulatory proteins. Actin microfilaments form a wide variety of structures: contractile rings, phagocytosis- and endocytosis-related structures, microvilli, cortex, adherens belts (associated with adherens junctions), filopodia, lamellipodia, and stress fibers. The ability of *H. pylori* to promote rearrangements of the actin cytoskeleton is well-established^[65-67]. The most evident demonstration of this is the so-called hummingbird phenotype, comprising a change in the epithelial cell shape to the characteristic elongated morphology of *H. pylori*-infected cells *in vitro*. This phenotype is thought to be linked to cancer cell migration and invasive growth *in vivo*^[68]. The hummingbird phenotype involves the formation of stress fibers and protrusions, the disruption of cell-to-cell adhesions, and the deregulation of focal adhesions between the cell and the ECM.

The basic mechanisms by which *H. pylori* changes the dynamics of the actin cytoskeleton during cell migration have been reviewed in depth by Wessler *et al.*^[69]. Briefly, *H. pylori*, via cag-PAI type-4 secretion system (T4SS; especially CagL) and CagA, is able to modify the host cell's signaling networks. On the one hand, CagL binds β 1 integrins, thereby stimulating the focal adhesion kinases (FAKs) and the Src-family kinases (SFKs); meanwhile, CagA activates the Abl-kinase. FAK, SFK, and Abl activate Crk, which in turn activates Rac1, which then promotes the assembly of actin filaments *via* activation of the Arp2/3 complex, contributing to cell motility. On the other hand, upon injection into the host-cell cytosol,

CagA is phosphorylated by SFK (c-Src) and binds Shp-2 and Csk, which then inhibit SFK in a negative feedback loop. Inhibition of SFK induces dephosphorylation of actin regulatory proteins, such as ezrin, vinculin, and cortactin. Cortactin stimulates the actin nucleation activity of Arp2/3 and, upon *H. pylori*-induced dephosphorylation, accumulates at the tip of the cellular protrusions and colocalizes with F-actin^[70].

The serine/threonine kinase polarity-regulating kinase partitioning-defective 1b (PAR1) participates in the CagA-mediated remodeling of the actin cytoskeleton. PAR1 inhibits the formation of stress fibers and cortical actin in the cell periphery. Kikuchi *et al.*^[71] showed that the physical interaction between the CagA multimerization sequence and PAR1b, the isoform present in gastric epithelial cells, is crucial for the stable binding of CagA and Shp-2. In fact, a second study found that CagA indirectly activates RhoA-dependent formation of stress fibers by impairing PAR1b-mediated inhibition of RhoA^[72]. These results were elegantly combined in a model that proposes a link among cell polarity regulation, the hummingbird phenotype, and actin cytoskeleton^[73]. More specifically, upon cell polarity loss of the epithelial cell, PAR1b and aPKC are relocated, resulting in the establishment of a front-to-rear polarity in which these two molecules are asymmetrically distributed, with PAR1b localized in the rear part of the migrating cell.

The binding of CagA to PAR1b modifies this program by perturbing PAR1b localization, which translates into loss of its kinase activity, lifting of the repression of RhoA, and formation of stress fibers; the salient manifestation of this is the hummingbird phenotype^[73]. The affinity of CagA for PAR1b and formation stress fibers increases proportionally to the number copies of the CagA-multimerization (CM) domain present in CagA, which is seemingly higher in East Asian CM than in Western CM and differs in five amino acid residues^[74].

Podosomes are dot-like structures of densely packed F-actin and serve as regulatory proteins by their capacity to degrade ECM components due to the presence of MMPs within. It has been shown in a model of primary hepatocytes and hepatoma cell lines that *H. pylori* can enhance the formation of podosomes by the induction of inflammatory cytokines such as TGF β ^[75], thus providing additional evidence of the capacity of *H. pylori* to modify actin structures. Actin-remodeling activity has also been described in another *Helicobacter* species, *H. pullorum*. Its cytolethal distending toxin, responsible for the cytopathological effects observed upon infection, induces actin cytoskeleton remodeling that is accompanied by delocalization of vinculin and up-regulation of cortactin in large, cortical actin-rich lamellipodia^[76].

Another important component of the cellular cytoskeleton is the microtubules. Structurally, they are formed by tubulins and regulated by microtubule-associated proteins. The microtubular network organizes the cell movement of organelles and is part of specialized structures such as cilia, flagella, mitotic spindles, cen-

osomes, and basal bodies. During cell migration, the small Rho-GTPase protein Cdc42 controls the actin microfilaments in the cell migration front and binds PAR6. The Cdc42-PAR6 dimer recruits the microtubule-regulating dynein/dynactin complex, which directs the machinery of the secretory pathway to the migration front. Importantly, this facilitates the delivery of integrins and other proteins that mediate the interaction with the ECM to the sites of migration.

Although not many, some studies have addressed the role of *H. pylori* infection in microtubule regulation in the context of cell migration. Slomiany and colleague^[77], for example, concluded that *H. pylori* lipopolysaccharide induced the secretion of MMP9 in a primary culture of murine gastric mucosal cells. In that study, the authors also found an accompanying increase of microtubule stabilization. Presumably, those changes are modulated by ghrelin and involve the activation of PKC δ and SFK.

Focal adhesions provide the structural link between the stress fibers and the ECM. They need to be dynamically assembled and disassembled in order to allow cell migration. *H. pylori* impairs focal adhesion release during cell migration, which leads to the characteristic elongation of infected cells^[68]. Paxillin, a multidomain protein that acts as an adaptor between the cytoplasmic tail of integrins and the actin cytoskeleton, has been designated as the convergent point of the epithelial growth factor receptor, FAK/Src, and PI3K/Akt signaling pathways in the context of *H. pylori* infection^[78]. Paxillin phosphorylation is dependent on the presence of a functional Cag-PAI or OipA. The phosphorylated paxillin was localized along the elongations, suggesting a role in the formation of stress fibers^[78].

PA system and *H. pylori*

The PA system comprises a few proteins that, by acting in sequence, lead to the conversion of zymogenic plasminogen into its active enzymatic form, plasmin. Extravascular activation of plasminogen is controlled by the urokinase-type plasminogen activator (uPA), its receptor (uPAR), its inhibitor PAI-1, and α_2 -antiplasmin. Besides degrading major ECM proteins (e.g., fibrin, fibronectin, laminins, and vitronectin), the generated plasmin also releases latent growth and angiogenic factors sequestered in the matrix^[79,80]. The expression of uPA, uPAR, and PAI-1 under normal homeostatic conditions is almost undetectable; however, in cancer and other pathologies, their expressions increase significantly^[81]. An important body of evidence correlates uPAR expression in cancer lesions with invasive and metastatic disease. Accordingly, high levels of uPAR in tissue and plasma are associated with poor patient survival in various types of cancer, including GC^[82-84]. Most of these reports have focused on uPAR, since this receptor is crucial for the initiation of the sequential series of events that ultimately result in the activation of plasminogen.

As already mentioned, *H. pylori* has been linked to

the induction of members of the PA system, primarily uPAR. Part of the experimental evidence supporting this phenomenon comes from *in vitro* studies, for example global gene-expression analyses ranking uPAR among the top up-regulated genes in AGS and T84 cell lines, when co-cultured with *H. pylori*^[85-87]. This has been confirmed by more specific *in vitro* studies, showing that in co-cultures, the bacterium rapidly induces uPAR expression in GC cell lines^[88-91]. A few of these reports indicate that uPAR induction is predominantly linked to CagA-positive strains^[87,89]. The potential connection between *H. pylori* and uPAR induction has also been documented in non-neoplastic tissue adjacent to GC lesions^[92] and in gastric biopsies from healthy patients who are infected with the bacterium^[93]. Interestingly, it has been reported that the expression of uPAR in neoplastic tissue may be correlated with the presence of *H. pylori* in adjacent non-neoplastic tissue^[94].

The link between *H. pylori* and uPAR has been systematically investigated in a mouse model of *H. pylori*-induced gastritis (Figure 3)^[95]. In this model, uPAR expression is up-regulated very early in response to the infection and increases progressively during the course of infection, and this is reverted to its physiological baseline levels if *H. pylori* is eradicated by antimicrobial therapy^[95]. Additional experiments in this model suggest that uPAR expression is directly induced by the bacterium (and Alpizar-Alpizar, unpublished results)^[95]. It is not possible to rule out, however, that uPAR induction in murine gastric epithelium is a consequence of the inflammatory reaction against *H. pylori*.

A few signaling pathways and transcription factors have been proposed as potential inducers of uPAR in cancer; however, much less is known about the mechanisms of induction in response to *H. pylori*. Studies in cancer cell lines have found that the NF- κ B can drive uPAR expression by direct binding to specific sequences within the regulatory region of the gene encoding uPAR^[96] or indirectly via HIF1 α activation^[97]. It is well known that *H. pylori* infection can lead to the activation of NF- κ B^[36,98]. Therefore, NF- κ B is a likely transcriptional inducer of uPAR in epithelial cells of *H. pylori*-colonized mucosa, both in human and mouse. *In vitro* evidence supports this idea^[88], but no experimental data have been generated *in vivo*.

AP-1 is another transcriptional regulator that is activated by *H. pylori* infection^[36] and has been implicated in the induction of uPAR in cancer^[99,100]. Thus, AP-1 may explain the potential connection between these two parameters^[90]. Both NF- κ B and AP-1 can be activated via the Ras-ERK MAPK signaling pathway^[99,101]. This pathway is often manipulated by *H. pylori*^[36], which makes it an interesting study target to gain further insight about the mechanism of induction of uPAR in the gastric epithelium colonized with *H. pylori*.

MMPs and *H. pylori*

The MMP family comprises more than 23 zinc-depen-

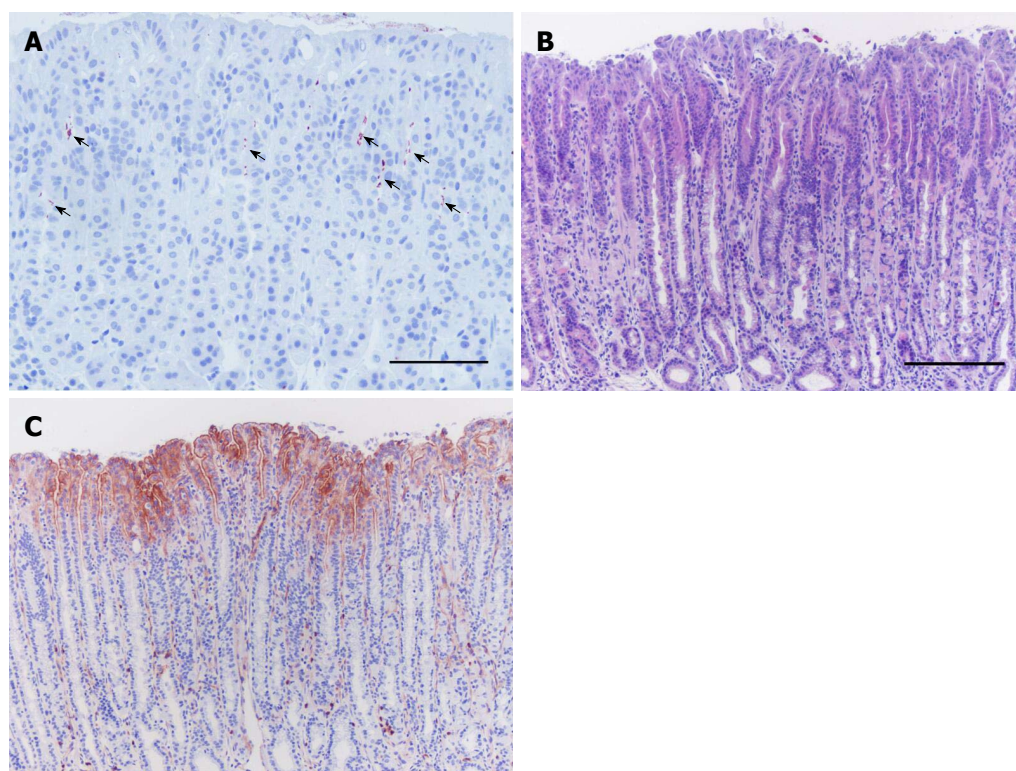


Figure 3 Plasminogen activator receptor induction in gastric epithelial cells in response to *Helicobacter pylori* infection. Stomach tissue sections of a mouse infected with *H. pylori* and euthanized 14 wk after inoculation processed for immunohistochemistry against *H. pylori* (A) and uPAR (C), and with H&E staining (B). Clusters of *H. pylori* bacteria (arrows) are observed in the upper third of the gastric glands along the gastric epithelium of the mouse stomach (A). Histopathological alterations are seen, including inflammation and mucous metaplasia (B). uPAR expression becomes evident at the apical membrane of foveolar epithelial cells in the corpus epithelium of *H. pylori*-colonized mice, such as the representative immunohistochemistry staining shown here (C). uPAR-positive scattered neutrophils are seen in the microphotograph (C) since they constitutively express this molecule. Scale bars: A: 100 μ m; B and C: 200 μ m. *H. pylori*: *Helicobacter pylori*; H&E: Hematoxylin and eosin; uPAR: Plasminogen activator receptor.

dent endopeptidases, subdivided into eight groups according to structural characteristics^[42,102]. MMPs are synthesized in the form of zymogens (pro-MMPs) by several cell types of the tumor microenvironment; and, when released to the extracellular space, they become activated by other proteases, including MMPs themselves and plasmin^[42]. Besides their role in invasion and metastasis, MMPs are involved in other aspects of tumor biology. The degradation of ECM constituents results in the liberation of sequestered growth, proliferative and angiogenic factors but also in the generation of ECM-derived peptides with similar biological properties to those factors. Some MMPs can cleave membrane-bound growth factor precursors, thus releasing their active form, for example TGF β ^[42]. Elevated expression of several MMPs has been consistently correlated with poor cancer patient survival in several types of cancer, including GC. Of note, a few MMPs actually inhibit malignant transformation and tumor growth, including MMP8, MMP12, and MMP26^[103-107].

The possible connection between *H. pylori* infection and induction of MMPs (*e.g.*, MMP2, MMP3 and MMP9) in gastric epithelial cells has been suggested; however, the most compelling evidence is probably for MMP7. MMP7 enhances tumor formation in rodents^[108], and it is particularly interesting in the context of the gastric

carcinogenesis because its expression is increased in human GC lesions^[109,110]. In human gastric cell lines co-cultured with *H. pylori*, it was found that cag-PAI-positive strains augment the levels of MMP7 up to 7-fold compared to uninfected controls or to cells incubated with specific isogenic mutant strains^[111]. According to that report, the induction of MMP7 in the *in vitro* system was dependent on the activation of ERK 1/2 and required an active interplay between viable bacteria and epithelial cells^[111]. That study also evaluated the expression of MMP7 in gastric biopsies of human patients and found that it was over-expressed in epithelial cells of gastritis-affected individuals infected with CagA-positive strains^[111], which has also been previously documented by an independent report^[112].

These observations served as the driving force for conducting subsequent investigations in MMP7 knockout mouse models. Such studies concluded that gastric inflammation and epithelial cellular turnover are substantially increased in MMP7-deficient mice infected with *H. pylori*, compared to their wild-type counterparts^[113,114]. It is speculated that over-expression of MMP7 in response to *H. pylori* colonization may be a mechanism to protect the gastric mucosa from damage and development of lesions that could ultimately result in GC^[112,113]. Nevertheless, it is also proposed that sus-

tained expression of MMP7 in the gastric epithelium could lead to malignant transformation^[112]. In fact, a few studies suggest that MMP7 proteolytically cleaves specific pro-apoptotic molecules, such as Fas ligand, from tumors cells, thus promoting tumor survival^[115,116].

CONCLUSION

H. pylori is a determining factor in the development of GC, due to the multiple ways in which it manipulates the host gastric epithelial cells. A key aspect of carcinogenesis is the acquisition of invasive capacities, and *H. pylori* could modulate several factors associated with invasion. A number of bacterial virulence factors may be of relevance in the manipulation of cellular and molecular programs that lead to increased invasive behavior; however, Cag-PAI stands out as a major orchestrator in hijacking these host cell pathways.

A number of key effectors of the EMT and cell polarity are deregulated in response to *H. pylori* infection. The two processes enhance cell motility and regulate the attachment of preneoplastic cells to the ECM and to other cells. This finally translates into an increased versatility of the cells to initiate the invasive process and adapt to the physiological changes suffered by the cell through the dedifferentiation induced by EMT. The acquisition of stem-like properties is a pivotal event that results from the activation of the EMT programs in response to *H. pylori*, since it confers the cells with augmented capability of survival and proliferation.

The induction of members of the PA system and MMPs by *H. pylori* could have important implications in the genesis of GC, given the wide array of aspects in which these molecules participate. Particularly interesting is the fact that this bacterium up-regulates the expression in non-neoplastic gastric mucosa of the uPAR, a protein that until now has been implicated in processes related to late stages of cancer development and progression, and has been correlated with the prognosis of cancer patients in general.

Altogether, the findings reviewed here show that *H. pylori* alters a fundamental process in gastric malignant transformation and invasiveness. Although we have discussed aspects related to EMT, cell polarity and ECM remodeling as independent processes, there are several points of interconnection among them (Figure 2). For instance, some factors implicated in the activation of EMT programs that are deregulated by *H. pylori* lead to the induction of MMPs and changes in cytoskeletal reorganization. Some of these proteinases, in the meantime, are capable of activating mediators of the EMT and cell polarity programs.

Therefore, the link between *H. pylori* and cell invasive properties is complex and an exciting open area of research where many aspects remain far from being clear. For instance, there is a need to gain further insight on how and under what circumstances *H. pylori* manipulates regulatory networks controlling the EMT and stem-cell programs. Also, it is important to unravel

the cellular and molecular mechanisms underlying the induction of members of the PA system and MMPs in *H. pylori*-colonized gastric epithelium.

Elucidation of the key orchestrators governing these invasion-related programs is crucial to understanding the implications that these processes may have for the survival of the bacterium or in the pathological context. All this information could be of relevance for identifying individuals with an increased risk of GC, who may require *H. pylori* eradication therapy, especially in countries with limited resources and high prevalence of this bacterial infection. Finally, this may contribute to prediction of pre-neoplastic lesions that are more likely to progress in the pathogenic series of steps to malignancy, which may be of relevance to reducing GC burden.

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