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REVIEW

Role of *Helicobacter pylori* infection in pathogenesis of gastric carcinoma

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Abstract

Gastric cancer (GC) is one of the most common carcinoma and the second leading cause of cancer-related deaths worldwide. *Helicobacter pylori* (*H. pylori*) infection causes a series of precancerous lesions like gastritis, atrophy, intestinal metaplasia and dysplasia, and is the strongest known risk factor for GC, as supported by epidemiological, preclinical and clinical studies. However, the mechanism of *H. pylori* developing gastric carcinoma has not been well defined. Among infected individuals, approximately 10% develop severe gastric lesions such as peptic ulcer disease, 1%-3% progresses to GC. The outcomes of *H. pylori* infection are determined by bacterial virulence, genetic polymorphism of hosts as well as environmental factors. It is important to gain further understanding of the pathogenesis of *H. pylori* infection for developing more effective treatments for this common but deadly malignancy. The recent findings on the bacterial virulence factors, effects of *H. pylori* on epithelial cells, genetic polymorphism of both the bacterium and its host, and the environmental factors for GC are discussed with focus on the role of *H. pylori* in gastric carcinogenesis in this review.

Key words: *Helicobacter pylori*; Virulence factors; Gastric cancer; Genetic polymorphism; Environmental factors

Core tip: It is important to gain further understanding of the pathogenesis of *Helicobacter pylori* (*H. pylori*) infection for developing more effective treatments for this common but deadly malignancy. The recent findings on the bacterial virulence factors, effects of *H. pylori* on epithelial cells, genetic polymorphism of both the bacterium and its host, and the environmental factors for gastric cancer are discussed with focus on the role of *H. pylori* in gastric carcinogenesis in this review.

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INTRODUCTION

Gastric cancer (GC) is one of the most common malignancies globally[1]. The risk factors for GC consist of *Helicobacter pylori* (*H. pylori*) infection, genetic and environmental factors[1]. *H. pylori* mainly colonized in human stomach, has coexisted with humans for nearly sixty thousand years[2]. The outcome of infection is affected by the environmental and genetic factors, the infection in most individuals does not develop distinct disease or even become beneficial, leading to the hypothesis that *H. pylori* might be commensal[3]. However, accumulating evidences support that *H. pylori* infection cause a list of diseases, ranging from gastric to extra-gastric diseases, from chronic gastritis to gastric carcinoma, and thus this bacterium is recognized as the Class Ⅰ carcinogenic pathogen in human with less than 3% of the infected eventually suffering GC[3].

Mechanism of *H. pylori*-associated gastric carcinogenesis has not been well defined. *H. pylori* infection commonly lasts for decades, provoking a series of histological changes including destruction of intercellular junctions, apoptosis and proliferation of epithelial cells and malignant transformation[4,5]. The genotypes of *H. pylori* strains, host genetic polymorphisms, environmental factors like high salt diet, smoking habit and certain gastric commensal organisms have been determined to be associated with occurrence of GC[6]. *H. pylori* genetic polymorphisms, effects of specific *H. pylori* products on gastric epithelium and cellular signaling process have been intensively investigated in recent decades[6]. This review is performed to discuss the role of *H. pylori* in gastric carcinogenesis.

H. PYLORI VIRULENCE FACTORS

Studies on *H. pylori* heterogeneity have proved that the strongest virulence factors were amongst the genes within the *cag* pathogenicity island (PAI).

CagA

CagA, a highly immunogenic protein, is encoded at one end of the *cag* PAI, which encode the components to form the type Ⅳ secretion system (T4SS)[7]. As a component of T4SS, CagL protein binds to and activates the integrin $\alpha5\beta1$ receptor on gastric epithelial cells and triggers CagA delivery into the target cells[8], CagM, along with CagX and CagT, forms an outer membrane-associated T4SS subcomplex[9], CagX and CagT interact directly[10]. As reported, CagA also facilitates its translocation into host epithelial cells by T4SS-induced externalization of phosphatidylserine from inner leaflet of the cellular membrane[8,11]. Recent studies demonstrated that fibronectinand peptidoglycan was also transported into epithelial cells by T4SS, suggesting that T4SS might have more CagA-independent functions than its ability to inject CagA[10]. CagA and CagM are important for assessing virulence of *H. pylori* strains.

H. pylori strains harboring the *cag* PAI or producing CagA are related to enhanced inflammation and risk of ulcers and carcinoma[12]. CagA contributes to myriad signaling alterations, which profoundly affects physiology of host epithelial cells. The Glu-Pro-Ile-Tyr-Ala (EPIYA) motifs in CagA are phosphorylation sites and play crucial roles in pathogenesis of *H. pylori* infection[13,14]. Once inside host cells, CagA is tyrosine phosphorylated by Src and Abl kinases at EPIYA motifs, and binds the SH2 domain of the SHP-2 phosphatase involved in transduction of signaling[15,16]. Phosphorylated CagA triggers the cellular signaling pathways leading to expression of proinflammatory cytokines and chemokines, and deregulates the signaling pathways that control host cell shape, adhesion and transformation[17,18]. Unphosphorylated CagA interacts with certain intracellular proteins, up-regulate production of proinflammatory cytokines, provoke mitogenic responses and disrupt intercellular junctions and epithelial cell polarity[17,19]. Additionally, CagA intoxicates dendritic cells leading to impaired activation, decreased inflammatory cytokine production and Th1 immune response[20]. Recently, it was confirmed that *H. pylori* infection resulted in rapid association of the virulence factor CagA with the c-Met receptor, activation of signaling and epithelial proliferation[21].

Vacuolating cytotoxin A

Vacuolating cytotoxin A (VacA) contributes to multiple structural and functional alterations of epithelial cells. After secretion by the bacterium through the type Ⅴ secretion system, VacA binds to host cells interfering with endosomal maturation and leading to vacuolation, enhances leakage of nutrients by destruction of barrier function at tight junctions of epithelial cells, provokes mitochondrial damage and cell apoptosis, which improves *H. pylori* growth[22-24]. Recent studies proved that VacA could disrupt phagocytosis, interfere with antigen presentation, restrain T cell activation *in vitro* and inhibit T cell proliferation independing of NFAT (nuclear factor of activated T cells) activation or IL-2 expression[25-27]. These effects of VacA on the immune system may explain how *H. pylori* evades adaptive immune responses to establish persistent infection.

BabA and SabA

Adherence to epithelial cells is important for *H. pylori* colonization and delivery of virulence factors to host cells[6]. BabA and SabA are two sialic acid-binding adhesins variably expressed by *H. pylori*. Among *babA* and *babB* genes, only the *babA2* allele possesses active

function[6,28]. BabA can bind to sialyl-Lewis x/a antigens and the Lewis b ABO blood group antigen (Leb), which are mainly distributed in red blood cells and certain epithelial cells[29], and this binding activity is commonly present in CagA positive strains[30]. Adherence mediated by BabA enhances the ability of T4SS to contact host cells, thus strengthen inflammatory response[31]. BabA binding to Leb contributes to gene mutations through formation of double stranded DNA breaks in host cell lines[32]. SabA can facilitate colonization in patients lacking Leb by binding to the sialyl-Lewis antigens[33], and mediate binding of *H. pylori* to sialylated structures of neutrophils[34]. The data suggest that BabA and SabA might be involved in carcinogenesis as abundance of sialyl-Lewis antigens is commonly enhanced in inflamed or cancerous gastric tissues[35].

OipA

OipA is an inflammation-related outer membrane protein, and the functional *oipA* gene is associated with more severe clinic outcomes[36,37]. *OipA* is commonly expressed together with CagA in *cagA* positive strains, which make it rather difficult to identify the effects of *oipA* alone in *H. pylori* infected human body or animal modules[38]. OipA expression is linked to increased production of proinflammatory cytokines like IL-8, IL-1, IL-17 and TNFα[39] as well as other host effector proteins including those associated with GC[40]. OipA can activate β-catenin, and mutant *H. pylori* strains lacking OipA decrease nuclear translocation of β-catenin, while tumorigenesis can be depressed by inactivating *oipA* of *H. pylori* strain in experimental animals[33,37]. These data suggest that OipA might take part in gastric carcinogenesis[33].

Gamma-glutamyl transpeptidase

Gamma-glutamyl transpeptidase (GGT) is mainly found in outer membrane vesicles of *H. pylori*, and has been proved to be related to enhanced levels of hydrogen peroxide and IL-8 production in epithelial cells and *H. pylori*-associated diseases[41-43]. GGT accelerates glutathione degradation, pro-oxidant compounds and reactive oxygen production[41]. GGT adjusts IL-8 expression by depletion of glutamine[41]. These findings indicate that GGT plays a significant role in *H. pylori*-related chronic inflammation and tissue damage.

It should be noted that interaction of the factors commonly exists *in vivo*, actions that a virulence factor take under the conditions with presence of other virulence factors might be different from those observed *in vitro*[44]. The influence of interactions between virulence factors in multifactorial pathogenesis is still uncertain. The main virulence factors in pathogenesis of *H. pylori* infection are shown in Figure 1[6].

EFFECTS OF *H. PYLORI* ON GASTRIC EPITHELIAL CELLS

Beside responsibility for digestive processes, the gastric epithelium has the function to protect underlying tissues from infection by pathogens[45]. *H. pylori* take specialized mechanisms to avoid host defense and adaptive immune for persistent colonization in human body, such as disruption of epithelial junctions, stimulation of cytokine production, overproliferation, DNA damage, apoptosis and cell transformation.

H. pylori disrupts junctions and polarity of epithelial cells

Intercellular apical junctions of epithelial cells are critical in keeping integrity of gastric epithelial barrier and essential cellular functions[25]. *H. pylori* disrupts epithelial tight junctions through binding to specific cellular receptors and stimulating the signaling pathways. As transported into epithelial cells through T4SS, CagA interacts with junction proteins like E-cadherin and ZO-1, and alters the tight or adherence junctions[25,46]. It has been confirmed that E-cadherin, a transmembrane protein, localizes at cell-to-cell junctions and interacts with β-catenin to form the E-cadherin/β-catenin complex, which play a key role in interaction of epithelial cells and stabilization of cellular architecture[46]. However, the complex is destabilized by translocated CagA in a phosphorylation independent manner during *H. pylori* infection[46]. As reported, CagA translocation is relevant to mislocalization of ZO-1 in epithelial cells[47,48]. Studies revealed that *H. pylori* altered expression and localisation of claudin-7, a cancer-associated tight junction protein, in gastroids and human epithelial cells, which was mediated by β-catenin and snail activation[49]. A recent study demonstrated that *H. pylori* diminished acid-induced tightening of cell junctions, affected the response of epithelial cells to acid, which took effects in inflammatory response and alteration of the barrier function[50].

H. pylori cause defect of epithelial cell polarity by targeting the epithelial adhesion receptors like E-cadherin and β1-integrin to modulate formation of cytoskeleton[51]. CagA disrupts polarity of epithelial cells through interaction with PAR1/MARK kinase[52]. As proved, an atypical protein kinase C (aPKC) contributes to disaggregation of PAR1 from tight junctions by phosphorylation of PAR1 at the junctions[52], and PAR1b binding to CagA restrains PAR1b activity and phosphorylation by aPKC to promote disruption of cellular polarity[48,52].

Induction of gastric epithelial cell autophagy or apoptosis

H. pylori not only colonize the mucus layer covering gastric mucosa, but also invade gastric epithelial cells, and even immunocytes[53]. Recent studies demonstrated that *H. pylori* induced autophagy of epithelial cells and phagocytes[53]. The autophagy of epithelial cells is modulated by *H. pylori*, and can be inducted by acute VacA exposure, and prolonged exposure to the toxin disrupts autophagy by preventing maturation of the autolysosome. The evidences support that *H. pylori*-

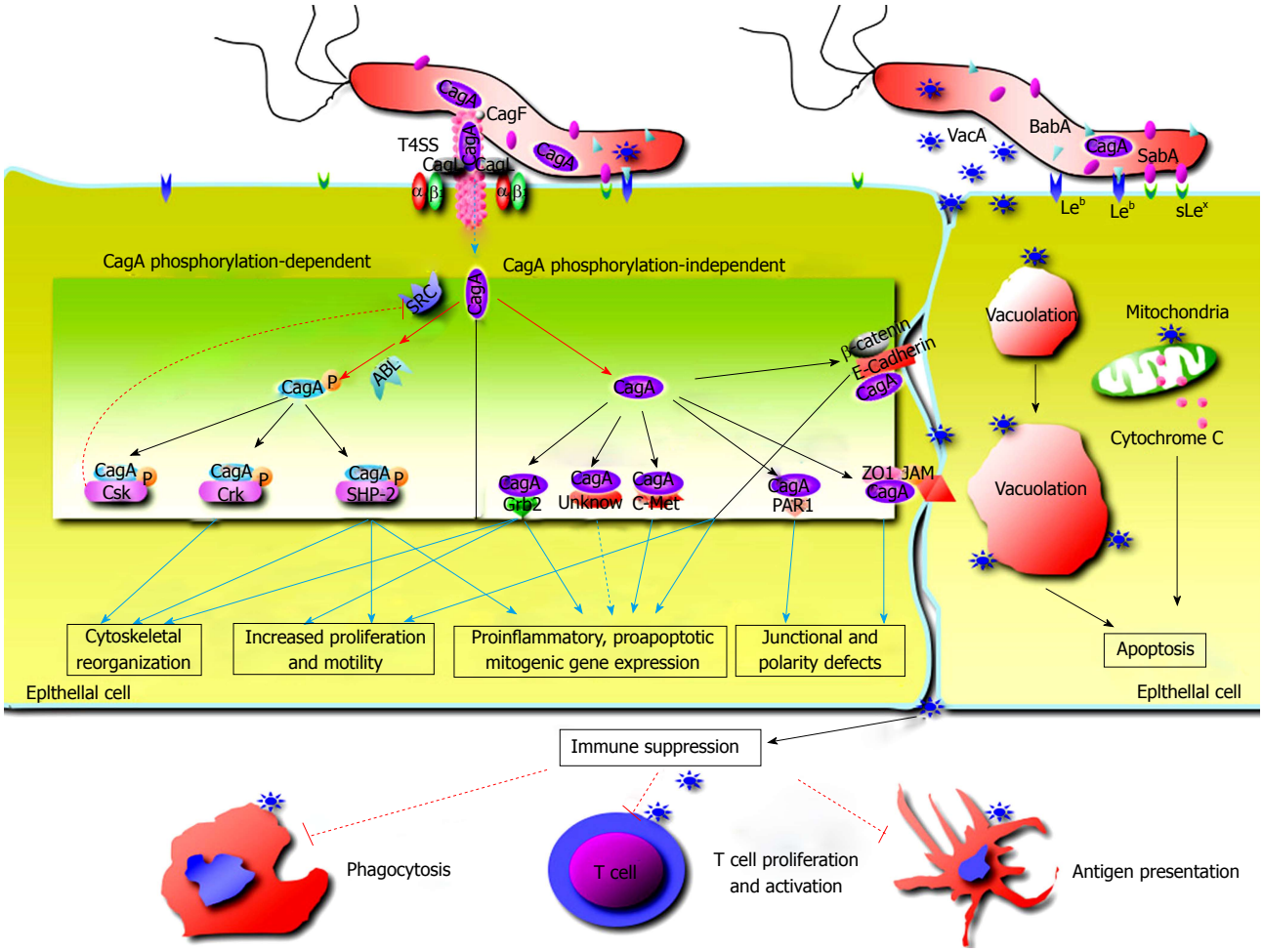

Figure 1 The roles of the main virulence factors in pathogenesis of *Helicobacter pylori* infection[6]. Adherence of *Helicobacter pylori* to gastric epithelial cells is mediated by BabA and SabA binding Leb and Lewis x/a respectively. CagA is translocated into epithelial cells through T4SS, and then tyrosine phosphorylated at EPIYA sites by Src and Abl kinases. CagA contributes to alteration of myriad signaling transduction, which affects host cell physiology with disruption of intercellular junctions, loss of cell polarity, promotion of inflammation, dysregulation of cellular apoptosis and proliferation. VacA inducts cytoplasmic vacuolation, apoptosis and immune suppression[6].

suppressed autophagy facilitates intracellular survival of this bacterium and generates an environment favoring carcinogenesis[54].

Rapid turnover of epithelial cells contributes to protect the epithelium from infection. *H. pylori* disrupts the balance of the proliferation and turnover of gastric epithelium to facilitate its survival[55]. Apoptosis is a regulated and conserved process in tissue, and takes the key role in tissue homeostasis[56]. *H. pylori* regulates the balance of epithelial cell apoptosis and proliferation for its reproduction[57,58]. The mechanism for this phenomenon remains to be well defined. The damage of gastric mucosa, stimulation of inflammatory immune responses by the enzymes like urease and VacA contribute to cellular apoptosis. The elevated level of free radicals produced by neutrophils and TH1 cytokines like IFN-γ in inflammatory response can damage DNA and induce apoptosis of epithelial cells[5,59]. *H. pylori* adhering to the epithelial surface also stimulate cellular apoptosis[60]. Studies demonstrated that human gastric epithelial cells sensitized to *H. pylori* confer susceptibility to TRAIL-mediated apoptosis through regulation of cellular FLICE-inhibitory protein activity and assembly of death-inducing signaling complex[61].

Cytokines secretion

The secretion of proinflammatory cytokines by gastric epithelial cells plays significant roles in pathogenesis of *H. pylori*-related gastric diseases. The cytokines involved in *H. pylori* infection include IL-8, IL-6, MCP-1, TNF-α, MIF, IL-1α, TGF-β, IL-1β and GMCSF[17]. The production of IL-8, a chemokine mediating accumulation of neutrophils, is related to the expression of CagA[17]. Further study confirmed that IL-8 and NF-κB expression was activated by urease B subunit[62], and the urease stimulates gastric epithelial cells to produce TNF-α and IL-6[63]. As reported, both *cag* PAI and OipA up-regulate IL-6 production in gastric epithelial cells[64]. Additionally, Th17 subsets are enriched in *H. pylori* infected mucosa[65]. The expression level of interleukin-17 (IL-17) has been observed to be up-regulated in gastric tissues of both human and animal during *H. pylori* infection, while

IL-17 can enhance expression of IL-8 in epithelial cells[66]. On the other hand, elevated levels of IL-21 and IL-23 expression in gastric mucosa induce and sustain IL-17 production[66]. Recently, a new clue for the pathogenesis of *H. pylori*-related gastric inflammation and GC is impairment of ghrelin synthesis in *H. pylori*-colonized stomach. Ghrelin, the ligand of growth hormone secretagogue receptor 1a, has immunoregulatory properties and function of certain inflammatory pathways inhibitor[67]. The defective ghrelin synthesis may contribute to sustain the ongoing inflammatory response in the gastric diseases[67].

Pro-carcinogenic responses

The mechanism underlying *H. pylor*-related gastric carcinogenesis remains unclear. CagA interacts with E-cadherin, deregulates β-catenin signal transduction and promotes gastric-to-intestinal transdifferentiation[47]. As observed, CagA translocated intracellularly binds to PAR1, destroys cellular junctions and polarity, and fosters carcinogenesis[48]. Development of gastric and hematological carcinoma has been observed in the mice that were genetically modified to express CagA[68]. Studies revealed that *cagA+/vacAs1+/vacAm1+H. pylori* strains promoted pathogenesis of intestinal metaplasia and gastric carcinoma[69].

Aditionally, *H. pylori* regulates expression of such toll-like receptors as toll-like receptor (TLR) 4 and TLR9 in epithelial cells during gastric carcinogenesis[70]. Caveolin-1 plays a protective role in immunologic injury caused by *H. pylori*[71]. Rapid association of the virulence factor CagA with the c-Met receptor, activation of signaling and induction of epithelial proliferation have been observed by using pluripotent stem-cell-derived gastric organoids[21].

GENETIC POLYMORPHISMS AFFECTING *H. PYLORI*-ASSOCIATED CARCINOGENESIS

H. pylori genetic variability

Genetic diversity of *H. pylori* has major contribution in the pathogenesis[72]. Studies have been conducted focusing on polymorphism of the main virulence factors, such as *cagA*, *vacA*, *oipA*, *iceA* and *hopQ*.

The highly polymorphic EPIYA motifs at the C-terminal of CagA are involved in pathogenesis of *H. pylori*-related gastroduodenal diseases[73]. CagA containing EPIYA motifs can activate the STAT3 pathway and promote cell migration[74]. The EPIYA motifs are distinguished by different amino acid sequences surrounding the EPIYA motif, and an increased number of CagA EPIYA-C sites confers a heightened risk for GC developing[75,76]. The sequences from Western and East Asian strains contain EPIYA-C and -D, respectively, and the strains with two segment C have more chances to develop GC than those with one[73]. The significantly higher prevalence of East Asian CagA in patients from Japan with *H. pylori* infection may be involved in the pathogenesis of GC[77].

Polymorphisms among the *vacA* alleles of *H. pylori* strains contribute to various levels of cytotoxicity, while variations in various regions can influence activity of VacA, including vacuolating activity[78,79]. It has been confirmed that vacuolating activity is highest in s1/m1 strains, *vacA* s1/m1 strains are closely relevant with GC in western countries[80,81]. Nevertheless, this situation is not universal worldwide, for example, s1/m1 strains in districts of Asia is irrelevant to clinical outcome[82,83].

Additionally, investigation of the prevalence of *oipA* and *iceA1/iceA2* positive strains among patients suffering from GC or gastritis results in that the frequency of *iceA1* allele in patients with GC is significantly higher than those with gastritis[72]. However, there is no significant difference in prevalence of *oipA* and *iceA2* genes among the two groups of patients ($P > 0.05$), suggesting the *iceA1* gene might take a role in pathogenesis of *H. pylori*-induced GC[72]. Studies also indicated that certain genetic types of *H. pylori hopQ* were closely related to GC[84].

Genetic polymorphism of H. pylori hosts

Polymorphisms in the genes encoding innate immune factors are involved in pathogenesis of *H. pylori*-related diseases, and the polymorphisms of cytokine genes cause inter-individual variation in cytokine responses which contributes to diversity of clinical outcome[85].

As reported, the risk of GC in many populations was affected by the polymorphism of the genes encoding IL-1β, TNFα, IL-8, IL-17 and IL-10 or their receptor antagonist[25]. An elevated risk of GC was observed in IL-8-251 AA or IL-10-1082 G genotype carriers with *H. pylori* infection[86]. IL-17 A/F plays critical function in inflammation and probably in cancer. Studies concluded that polymorphism of IL-17F was involved in susceptibility to GC[87].

Current evidences support that TLRs are play roles in both recognition of *H. pylori* and gastric carcinogenesis, and polymorphisms in genes involved in the TLR signaling pathways modulate the risk of GC[88].

Additionally, peroxisome proliferator-activated receptors may play roles in *H. pylori*-related gastric carcinogenesis[89]. The G/G variant rs2076167 is relevant to increased risk of GC in an animal model. The association between G/G variants of rs2016167 and GC is close among those consuming higher salt diet[89]. The insertion/deletion polymorphism of the angiotensin I-converting enzyme gene was recently proved to be linked to the pathogenesis and progression of human cancers[90]. As demonstrated, both bacterial and host gene polymorphisms affect oxidative stress and DNA damage, as thought to be a key mechanism in gastric carcinogenesis. The interaction of bacterial and host gene polymorphisms may become an explanation for why GC only occurs in a small proportion of *H. pylori*-infected individuals[91].

Table 1 Association between cagA status and tobacco smoking[98]

	N cagA neg	*N* cagA pos	OR	95%CI	OR[1]	95%CI
Smoking status at endoscope						
Non active smokers	34	31	1.00		1.00	
Active smokers	8	23	3.15	1.23-8.07	4.52	1.28-15.98
Smoking status						
Never	22	23	1.00		1.00	
Former smoker	12	8	0.64	0.22-1.86	0.36	0.09-1.53
Current smoker	8	23	2.75	1.02-7.43	3.24	0.84-12.47
P value for linear trend				0.067		0.123

[1]Adjusted for sex, age (≤ 50 years, > 50 years)[98].

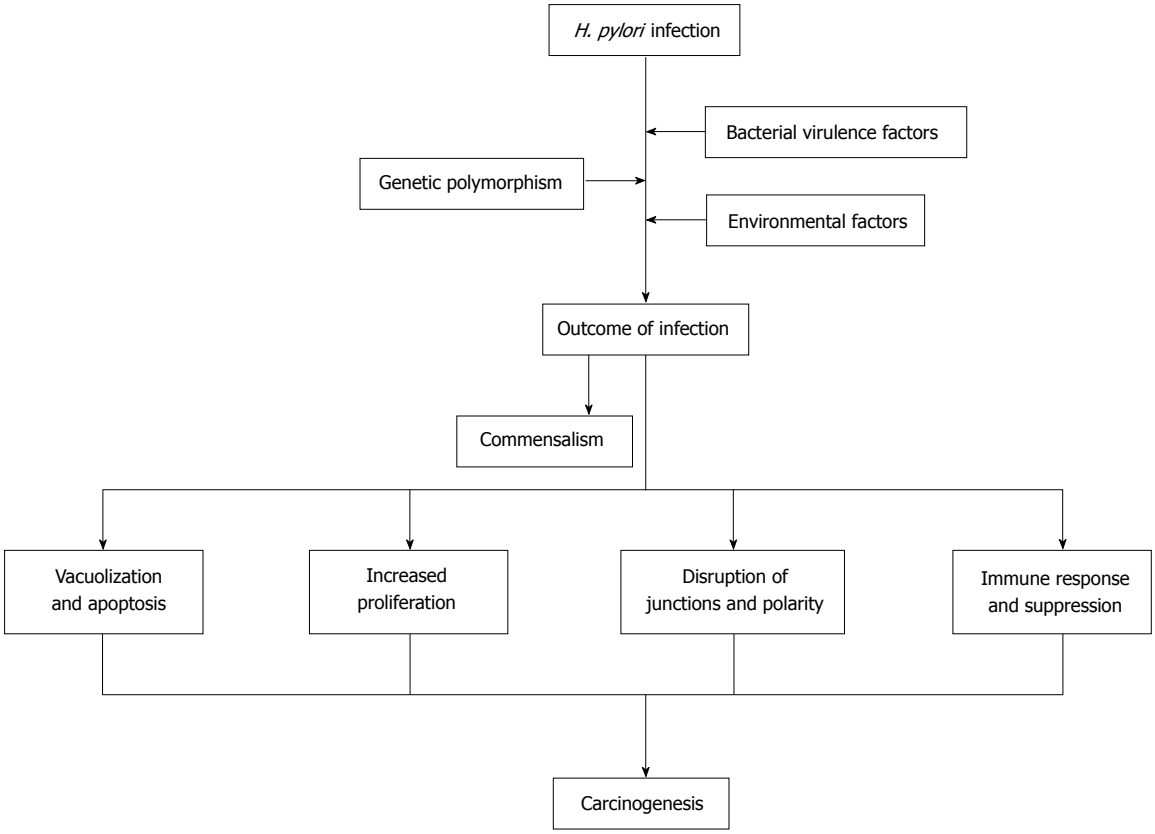

Figure 2 The pathogenesis of *Helicobacter pylori*-associated gastric cancer. The pathogenesis of *H. pylori*-associated GC is a multi-factorial process, its development depends on a combination of host, bacterial and environmental factors, and the pathological changes might progress in steps. *H. pylori*: *Helicobacter pylori*; GC: Gastric cancer.

ENVIRONMENTAL FACTORS IN *H. PYLORI*-RELATED GC

There are multiple ways by which *H. pylori* manipulates the host to lower the threshold for carcinogenesis, gastric microbiota, high-salt diet, smoking habit, low iron levels and use of proton pump inhibitors (PPIs) may enhance risk of *H. pylori*-associated carcinogenesis[92].

Gastric microbiota

Alterations of microbiota inhabiting human digestive tract can favor carcinogenesis[93]. Conventional wisdom espoused the dogma that pH values < 4 were able to sterilize the stomach, but since the discovery of *H. pylori*[94], a complex community of noncultivatable inhabitants have been uncovered in the stomach[95]. The interaction of gastric microbiota with *H. pylori* likely affects gastric immunobiology and the outcome of infection[95]. Data indicate that the microbial density in the normal stomach is low (10^1-10^3 CFU/g)[94], and the low bacterial densities within this portion of gastrointestinal tract is attributed to rapid peristalsis, low pH and/or high bile concentration[96]. The parietal cell loss caused by *H. pylori* infection leads to hypochlorhydria or even achlorhydria, thereby increase the risk of bacterial overgrowth and detrimental infection[97]. Alteration of gastric microbiota may promote the development of GC by up-regulating production of N-nitroso

compounds[93].

Smoking

Studies demonstrated that virulence factors like *cagA* and smoking might have synergistic effect in carcinogenesis of GC, and *cagA* genotype of *H. pylori* strains was closely related to active-smoking in population with *H. pylori* infection as shown in Table 1[98].

High salt diet

As evidenced, CagA expression is significantly upregulated when certain *H. pylori* strains are cultured in a medium of high salt concentrations. Through sequence analysis and site-directed mutagenesis, it was determined that salt-responsive *H. pylori* strains were more likely to contain two copies of TAATGA motif within the *cagA* gene promoter, while the strains containing only a single copy of this motif were less likely to possess properties of salt-responsive CagA expression[92,99]. However, another study showed that the severity of gastritis in *H. pylori* infected population might be unassociated with high-salt diet[100].

Iron levels

The iron level in the host has also been proved to manipulate the virulence potential of *H. pylori*. The bacteria harvested from gerbils with low iron levels were found to assemble more T4SS pili per bacterium, translocate increased amounts of CagA, and augment more IL-8 secretion compared to those isolated from gerbils with normal iron levels[101,102]. Furthermore, the *H. pylori* strains isolated from patients with low ferritin levels induce significantly higher levels of IL-8 compared to the strains from patients with the highest ferritin levels, suggesting that iron deficiency in the host might enhance the bacterial virulence and the risk for carcinogenesis of gastric tissues[101,102].

PPIs

It has been evidenced that long-term use of proton PPIs might aggravate corpus atrophic gastritis in *H. pylori*-infected patients[97]. The worsening atrophic gastritis contributes to development of gastric carcinoma, particularly owing increasing production of potentially carcinogenic N-nitroso compounds by the bacteria overgrowing under conditions of hypochlorhydria[97]. Hypergastrinemia induced by PPI administration might also promote the development of GC[97].

Di (2-ethylhexyl) phthalate

Di (2-ethylhexyl) phthalate (DEHP), as an essential additive in plastic manufacturing, has been used as plasticizer for many products including plastic food packaging[103]. Recent studies confirmed that DEHP was a teratogenic compound closely related to carcinogenesis[103]. DEHP may enhance *H. pylori* cytotoxicity, induce gastric epithelial cell apoptosis, disrupt the gastric mucosa integrity and promote pathogenesis of gastric carcinogenesis[103].

CONCLUSION

The genomes of *H. pylori* are highly diverse, multiple virulence factors take effects on host epithelium in various manners, including direct action and indirect action like eliciting immune response. Genetic polymorphism of host, dietary factors, smoking, gastric microbiota and long-term consuming of PPIs influence the progression of *H. pylori*-relate gastric lesion. The pathogenesis of *H. pylori*-associated GC is a multifactorial and multi-step process, and its development depends on a combination of host, bacterial and environmental factors as shown in Figure 2. It is important to further reveal the carcinogenesis of *H. pylori*-related GC in order to develop more effective treatments for this common but deadly malignancy.

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