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Role of polymorphisms in genes that encode cytokines and *Helicobacter pylori* virulence factors in gastric carcinogenesis

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Abstract

The *Helicobacter pylori* (*H. pylori*) infection is a determinant factor in gastric cancer (GC) development. However, the infection outcomes are variable and depend on both host and bacterial characteristics. Some host cytokines such as interleukin (IL)-1 β , IL-1Ra, IL-8, IL-10 and tumor necrosis factor- α play important roles in the host immune system response to the pathogen, in the development of gastric mucosal lesions and in cell malignant transformation. Therefore, these host factors are crucial in neoplastic processes. Certain polymorphisms in genes that encode these cytokines have been associated with an increased risk of GC. On the other hand, various virulence factors found in distinct *H. pylori* bacterial strains, including cytotoxin-associated antigen A, vacuolating cytotoxin, duodenal ulcer promoting gene A protein, outer inflammatory protein and blood group antigen binding adhesin, have been associated with the pathogenesis of different gastric diseases. The virulent factors mentioned above allow the successful infection by the bacterium and play crucial roles in gastric mucosa lesions, including malignant transformation. Moreover, the role of host polymorphisms and bacterial virulence factors in gastric carcinogenesis seems to vary among different countries and populations. The identification of host and bacterium factors that are associated with an increased risk of GC development may be useful in determining the prognosis of infection in patients, what could help in clinical decision-making and in providing of an optimized clinical approach.

Key words: *Helicobacter pylori*; Virulence factors; Cytokines; Gene polymorphisms; Gastric cancer

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Core tip: Various polymorphisms in host genes that encode cytokines and *Helicobacter pylori* virulence factors have been associated with different tendencies of gastric diseases development. Several reviews have been written on the role of host and bacterial isolated factors in gastric carcinogenesis. However, only a small amount of reviews unites the important characteristics of both bacterium and host in carcinogenesis. General overviews about polymorphisms in genes that encode cytokines are also scarce. We aimed to join the main polymorphisms in genes that encode cytokines and bacterial virulent factors related to gastric carcinogenesis and to provide a broad overview about these themes.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram negative bacterium, which inhabits the gastric epithelial tissue of most people in the world^[1], and it is considered a determinant factor in the initiation of gastric carcinogenesis^[2]. Gastric cancer (GC) is one of the four most prevalent neoplasms and the second biggest cause of deaths in consequence of cancer worldwide^[3]. Despite the importance of *H. pylori* in gastric carcinogenesis, the development of GC only occurs in a minority of infected people, demonstrating that the infection outcomes are variable. It is believed that multifactorial precancerous processes associated with both host mucosal inflammatory response and pathogen characteristics are determinant in the severity of the disease^[4].

The host immune system response plays a crucial role in the outcomes of *H. pylori* infection. Polymorphisms in genes that encode cytokines have been reported and associated with the severity of gastric mucosa inflammation and GC development. Some of these determinant variations are present in genes that encode cytokines such as interleukin (IL)-1 β , IL-1Ra, IL-8, IL-10 and tumor necrosis factor (TNF)- α ^[5-13]. These polymorphisms are important aspects in understanding gastric carcinogenesis, since chronic inflammation induced by the bacterium is critical in the emergence and evolution of GC precursor lesions (Figure 1)^[14].

On the other hand, the virulence factors of *H. pylori* are determinant in the interaction with host cells. Cytotoxin associated antigen A (CagA), vacuolating cytotoxin (VacA), duodenal ulcer promoting gene A protein (DupA), outer inflammatory protein (OipA) and blood group antigen binding adhesin (BabA) are

some virulent factors that seem to be associated with different risks of GC development^[15]. Furthermore, *H. pylori* with EPIYA-D or more than one EPIYA-C segment in its *CagA* gene have been associated with a higher risk of gastric carcinogenesis^[16-20].

POLYMORPHISMS IN GENES THAT ENCODE CYTOKINES AND GASTRIC CARCINOGENESIS

Gastric carcinogenesis is a process in which chronic inflammatory status plays a crucial role. The increase of inflammatory cytokine levels, due to *H. pylori* infection, seems to be determinant in the initiation and progression of GC^[12]. The intensity of the expression of cytokines can be modified by functional polymorphisms in the promoter regions of the genes, which has the potential to alter the affinity of transcription factors, interfering in the expression levels of the messenger ribonucleic acid (mRNA) of specific inflammatory mediators related to the susceptibility of GC initiation^[21].

IL-1

IL-1 is a family of cytokines that possesses 11 described members, among which IL-1 β and IL-1 receptor antagonist (IL-1Ra), combined with *H. pylori* infection, seem to be key factors in GC development^[22-24]. Signaling through the IL-1 receptor is a necessary event for the beginning and sustenance of various responses of the immune system^[25].

The promoter regions of *IL1B* and *IL1RN* genes, which encode IL-1 β and IL-1Ra respectively, have SNPs that modify the expression of the genes and affect the inflammatory response^[26]. These SNPs increase the IL-1 β /IL-1Ra ratio, which unleashes processes that result in gastric hypochlorhydria, favoring GC development^[15,27].

IL-1 β is an important cytokine for host-response to pathogens; however, this mediator can exacerbate damage during chronic diseases^[28]. High levels of IL-1 β in *H. pylori* infections lead to gastrin overexpression, increased gastric inflammation, hypochlorhydria, and gastric atrophy^[29]. Moreover, IL-1 β might promote neoplastic growth^[30]. The *IL1B* gene can be composed by three different SNPs: C-T base transition at IL-1B-511 (rs16944), T-C base transition at IL-1B-31 (rs1143627) and IL-1B-3954 (rs1143634), and all of them are strongly associated with increased production of proinflammatory cytokines, hypochlorhydria and increased GC risk, mainly intestinal type, among Caucasians, but not among Asians or Hispanics^[31-34].

IL-1Ra inhibits IL-1 α and IL-1 β by means of binding to IL-1 receptors. *IL1RN* possesses a changeable number of tandem repeats in intron 2, forming long alleles (IL1RN1) with 3-6 repeats or a short allele (IL1RN2) with 2 repeats^[35]. The IL1RN2 allele is associated with severe gastric lesions and higher risk for GC, besides raised IL-1 β expression in Caucasians^[33-36].

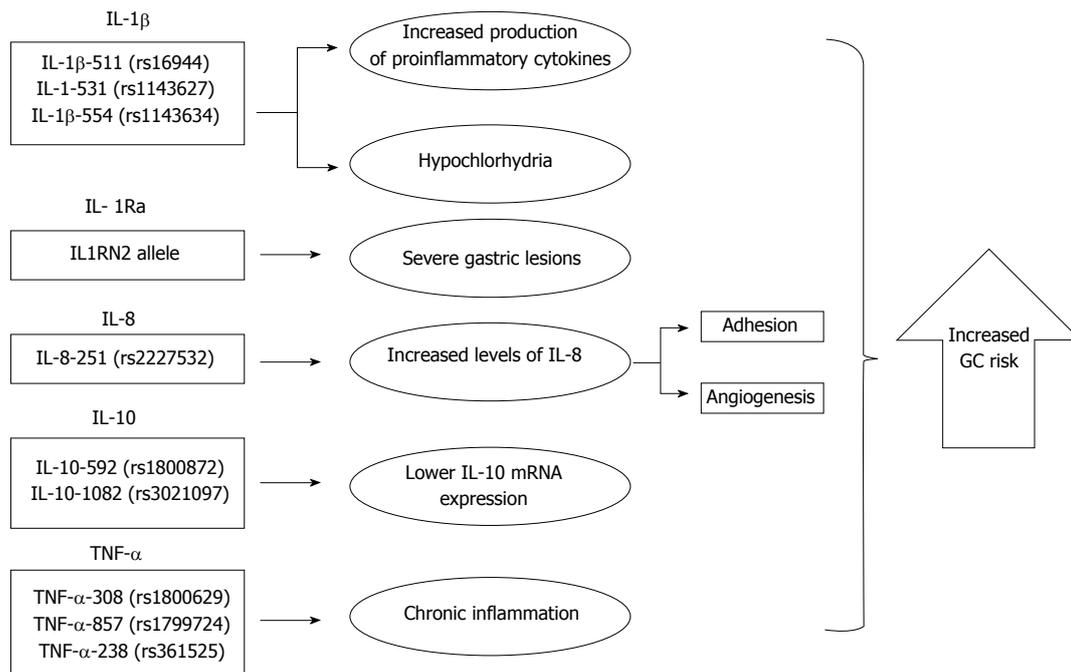


Figure 1 Potential functions of the host genetic polymorphisms in gastric carcinogenesis. IL: Interleukin; GC: Gastric cancer; TNF: Tumor necrosis factor.

IL-8

IL-8 is a potent cytokine that induces the directed migration of cells to inflammatory sites, acting as a chemoattractant^[37]. IL-8 secretion can be increased by different stimuli, such as live bacteria (including *H. pylori*) and lipopolysaccharides (LPS), besides others inflammatory cytokines, including IL-1 and TNF^[38]. The association of IL-8 with angiogenesis, adhesion and tumorigenesis have been related^[39,40].

The gene *CXCL8*, which encodes IL-8, is located on 4q12-21 chromosome and possesses four exons and three introns^[41]. An A/T SNP in the -251 position of this gene (*rs2227532*) has been associated with the development of various inflammatory diseases and cancer, including GC in Asians, but not in Europeans^[42,43]. Furthermore, the IL-8-251 A allele was related to increased levels of IL-8^[41].

IL-10

In opposition to the cytokines mentioned above, IL-10 is an anti-inflammatory cytokine, and it is involved in the cytotoxic response of inflammation and in cell downregulation. Moreover, this mediator prevents the production of pro-inflammatory cytokines, including TNF- α and IL-8^[44]. Some studies have demonstrated that SNPs, particularly IL-10-592 (rs1800872) and IL-10-1082 (rs3021097) alleles, might modulate transcriptional activation and affect IL-10 production in vitro. These IL-10 polymorphisms are related to lower mRNA expression of this cytokine and it have been associated with GC development in Asians^[45-48].

TNF- α

TNF- α composes the TNF/TNFR cytokine superfamily

and it is involved in maintenance and homeostasis of the immune system and host defense^[49]. However, this cytokine is related to various pathologic processes, including autoimmunity, chronic inflammatory processes and malignant disease^[50]. According to studies, TNF- α signaling through TNFR1 (TNF- α receptor) is important for gastric tumor development^[51,52].

Some SNPs in the TNF- α gene are related to increased expression of this cytokine. Among these polymorphisms, TNF- α -857 C/T (rs1799724), TNF- α -308 G/A (rs1800629) and TNF- α -238 G/A (rs361525) are the most studied ones. TNF- α -308 G/A was significantly associated with GC only in Caucasians, while TNF- α -857 and TNF- α -238 were related to an increased risk of gastric tumorigenesis in Asians, but not in Caucasians^[53-55].

H. PYLORI VIRULENCE FACTORS AND CARCINOGENESIS

The capacity of *H. pylori* bacteria to trigger a carcinogenic process is not limited to the intense immune response that they unleash, but it also depends on various bacterial factors that can start and modulate neoplastic processes^[56]. Different virulent factors found in distinct bacterial strains have been closely associated with the emergence of gastric carcinogenesis. However, genetic variations in genes that encode these virulence factors as well as geographic differences can influence the role of these proteins in GC emergence^[15].

CagA

CagA is encoded by the *cagA* gene, present in a DNA

segment containing 30 genes called *cag* pathogenicity island (*cag PAI*). Infections by strains containing CagA are more capable to induce carcinogenic processes, mainly those with EPIYA-D or more than one EPIYA-C segment^[57]. Various *cag PAI* genes are involved in the codification of elements of a pilus structure named type IV secretion system (TFSS), which has the function of transporting CagA from bacterium to the cytoplasm of the cells from gastric epithelium^[58].

After being injected into host cells by TFSS, CagA suffers tyrosine phosphorylation at a carboxi-terminal segment compound by distinct number of EPIYA (Glu-Pro-Ile-Tyr-Ala) regions. There are different EPIYA segments -A, B, C and D-, which contain distinct amino acids in their structure^[20]. EPIYA A and B segments are present in most CagA proteins and are followed either by 0-3 EPIYA-C segments in *H. pylori* strains from Occidental countries or by EPIYA-D segments in Eastern countries^[59].

Following EPIYA-C or EPIYA-D phosphorylation, an interaction between these segments and SHP-2 possessing SH2 domain occurs, unleashing SHP-2/mitogen-activated protein kinases (MAPK), ERK1, 2-JAK and STAT3 pathways^[20]. Cytotoxin associated antigen containing EPIYA-D or more than one EPIYA-C segment ties to SHP-2 more strongly, being more effective in the activation of the pathways mentioned above^[60]. This process, activated by CagA, leads to dysfunction of cell growth and of cell-to-cell contact inhibition, cell migration, epithelial cell elongation, and increase of epithelial cell turnover, increasing the propensity of acquirement of precancerous genetic changes by damaged cells^[61]. Furthermore, it was demonstrated that relatives of GC patients are more often infected by *H. pylori* strains with more than one EPIYA-C segment in CagA structure^[62]. Another study carried out by this same group, performed in a Brazilian population, showed that the host signal transducer and activator of transcription protein 3 (STAT3) rs7744166 polymorphism, as well as being infected by *H. pylori* with CagA containing more than one EPIYA-C segment, are independent predisposing factors for GC^[20].

VacA

VacA is another determinant virulence factor in *H. pylori* infection and in gastric carcinogenesis. Patients infected with VacA-positive *H. pylori* strains have a higher propensity for GC development when compared with patients colonized by VacA-negative strains, either in American or in Asian people^[63]. Particularly, individuals infected with *H. pylori* strains VacA s1, m1 and s1m1 had an increased risk for gastric carcinogenic unleash in Middle East, Africa and Latin America populations^[64]. The peptide mentioned above has only two functional domains in its structure. One of them, the p55-58 domain, has the function of binding to receptors of gastric epithelial cells. The other functional domain, p33-37, produces the cytotoxic effect^[65].

VacA is a 90 kDa exotoxin that is activated in a low pH environment^[66]. This toxin promotes the generation of numerous acidic vacuoles in gastric epithelial cell cytoplasm^[67]. In this process, VacA affects the structure and function of the membrane, the endoplasmic reticulum, the Golgi apparatus and the mitochondria, which can lead to cell death. Furthermore, vacuolating cytotoxin also plays an important role in the activation and suppression of the immune response^[68]. This peptide induces a powerful inhibition over T lymphocyte proliferation by means of an interaction with dendritic cells, which are reprogrammed to a tolerogenic genotype^[69]. The damage and the immunomodulation performed by this toxin contributes to the increase of gastric mucosa inflammation, ulceration and carcinogenesis in mammals^[68].

DupA

Unlike the other virulence factors mentioned in this article, DupA seems to be a protective condition for GC. The *dupA* gene is constituted by two homologue genes of *virB4*, *jhp0917* and *jhp091*, which constitute a continuous gene. The real function of the protein encoded by *dupA* is still obscure, however, its mechanisms seems to be related to the increase of the production of IL-8 in the gastric antrum, contributing to the development of gastritis that predominates in that gastric region, a process that leads to duodenal ulcer formation^[70]. DupA has been significantly associated with duodenal ulcer formation in Asian countries, but this relation was not observed in the Western population^[71]. Furthermore, DupA-positive *H. pylori* has been associated with eradication failure^[72].

OipA

OipA constitutes a group of peptides described as outer membrane proteins (OMPs), a *H. pylori* protein family composed of 32 components^[73]. OipA has been described as a better marker for severe clinical outcomes than CagA, since the infection by strains possessing OipA is an independent determinant risk factor of GC vs gastritis in Americans^[74,75]. OipA enhances IL-8 production and leads to an increased inflammation status of gastric epithelium. Moreover, it was observed that OipA could inhibit the maturation of dendritic cells in vitro, which might contribute to the immunomodulatory processes performed by *H. pylori*^[76].

BabA

babA is a gene that encodes an adhesin whom allows the specific binding to the b and H-1 Lewis antigens, which are expressed in the surface of the gastric mucosa cells^[77]. The adhesion of the *H. pylori* to the gastric epithelium mediated by blood group antigen binding adhesin (BabA) appears to play a critical function in the transference of bacterial virulence factors to the host cells. This process contributes to the development of tissue lesions, and a high correlation

of *babA*-positive strains of *H. pylori* with GC has been described^[78,79].

CONCLUSION

Despite the wide knowledge about host and *H. pylori* interaction developed since the discovery of its colonization in human stomach, many characteristics that contribute to the infection outcomes are still obscure. The understandings about host polymorphisms in genes that encode cytokines and bacterium virulence factors in GC development are important not only for the determination of patients' prognosis, but it is also a potential way for the development of new preventive and therapeutic strategies.

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