Chapter

Helicobacter pylori; a Way to Gastric Cancer?

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Abstract

Gastric cancer is one of the types of cancer that is associated with *Helicobacter pylori* infection. The infection starts in childhood, and 50–90% of the population in the world is infected. The clinical symptoms can be stomach pain, gastritis, atrophy gastric, and only 2–3% of the infected population developed gastric cancer. The majority of gastric cancers are adenocarcinomas. From Lauren's histological classification, gastric cancer is divided into two large groups: intestinal and diffuse. The cells that gives rise to them are different and the epidemiologic features and diagnosis are different according to gender and age; however; the survival rate is approximately of 5-years. Surgery is the only radical treatment, but the adjuvant treatment is chemotherapy and radiotherapy which unfortunately lead to only a modest survival benefit. On this review, we describe the major risk factors associated with the bacteria: cagPAI, CagA, VacA, HOPs, as well as host immune and inflammatory responses: immune cells, Toll-like receptors, cytokines, immune signal pathway, genetic predisposition, such as single nucleotide polymorphisms (SNP's) and environmental factors: age, high salt intake, diets low in fruit and vegetables, alcohol intake, and tobacco use. Finally, we included the interaction of all factors for the development of gastric cancer. Knowing and understanding the role of all factors in the development of gastric cancer will allow the implementation of better therapies and improve patient prognosis.

Keywords: *Helicobacter pylori*, inflammatory response, dysplasia, metaplasia, gastric cancer

1. Introduction

Helicobacter pylori is a Gram-negative bacterial pathogen that infects more than half of the human population worldwide. It is usually acquired during childhood and it is able to establish a lifelong chronic infection [1]. *H. pylori* is characterized by an exceptionally high genetic diversity and variability. Some pathogenic mechanisms include relatively inefficient DNA repair mechanisms as well as natural competence for transformation and the ability to integrate small fragments of homologous DNA into the chromosome. The species of Helicobacter are divided into large phylogeographic populations with distinct geographical distributions. In 22 countries in Central and South America and Asia, a prevalence of approximately 70% or higher around age 60 years was reported in the late 1990s and early 2000s, with a decreasing tendency in different time periods in most countries where data were available [1]. This text is a historical review of the data which exist on host-helicobacter interaction.

2. Virulent factors from *H. pylori* and its interaction with the host

2.1 Virulence factors and their association with gastric cancer

2.1.1 Cag Pathogenicity Island and Cag A

The major protein that was identified as a product of the multigene *cag* Pathogenicity Island (*cag*PAI) is CagA. The *CagPAI Island* has 27–31 putative genes and 20 genes encode to the type IV secretion system.

CagA is a protein considered an oncoprotein; it is translocated into gastric epithelial cells by the type IV secretory system of the pathogen, inducing multiple signaling cascades [1]. There are two distinct types of *H. pylori:* cagA-positive and cagA-negative strains. Only the CagA-positive strains induce the onco-transformations in animal models and contribute in the development of gastric cancer. The gene of *cagA* has different repeated sequences in the 3'region; each repeat region contains EPIYA motifs; its term describes specific sequence of amino acid (Glu-Pro-Ile- Tyr-Ala). If the first repeat region has two EPIYA motifs, they are called EPIYA A and EPIYA B; however, if there are two in the second repeat region, they are call EPIYA-C and EPIYA-D [2].

The CagA is injected into the host cell through the type IV secretion system (T4SS). In the cytoplasm, CagA is phosphorylated at its EPIYA motifs; CagA alters the host cell signaling in both manners, phosphorylation- dependent and phosphorylation-independent. After its translocation into the host epithelial cells, the EPIYA-motifs of CagA undergo tyrosine (Y)-phosphorylation via cellular kinases, such as Csk, c-Src, and c-Abl. The phosphorylated tyrosine interacts with the Src homology 2 phosphatase (SHP2) or with the adapter protein Grb2 and hinders cell–cell adhesion, cellular proliferation, IL-8 expression, and cellular elongation via the activation of cell signaling pathways, such as Ras–ERK MAP kinases (Rap1 → B-Raf → Erk) and Wnt-β-signaling [3].

Li et al., 2018 demonstrated that CagA stimulates YAP signaling pathway activation leading to gastric tumorigenesis in AGS cells. This in vitro result was also supported by the finding that *H. pylori* infection could enhance YAP expression activation together with the E-cadherin suppression in chronic gastritis tissues infected with *H. pylori* compared to *H. pylori* negative patients [4]. Infection with CagA-positive strains is thus associated with an increased risk of developing atrophic corpus gastritis compared to CagA-negative *H. pylori*-positive subjects [1]. The association with atrophy in the stomach is more in developed countries, but in developing countries, there is a balance of the immune response for there are co-infections with helminthes, with increased T regulatory cells and polarize inflammation to Th2 responses, which reduces gastric atrophy in *H. pylori*-infected subjects [5] (**Figure 1**). CagA has another target in the CDX1 cells, which is a home box transcription factor that plays an important role in the development of the human intestine. In an abnormal environment, CDX1 produces cell proliferation, invasion, and migration, induces the change from gastric characteristic to intestinal characteristics, and induces the stream cell-like phenotype. These cells have a Lrig-1 marker in their surface; a high number of steam-like cells is associated to premalignant lesions, such as atrophic gastritis and intestinal metaplasia, which develop resistance to chemotherapies [6, 7]. Some gastric cancer case–control studies have demonstrated that *H. pylori* and CagA positive increased risk in both intestinal-type gastric cancer and diffuse-type gastric cancer when compared with non-cancer control [8, 9].

The interaction of *H. pylori* with the environment of the host can be an important element in the infection. There are many environmental factors that may

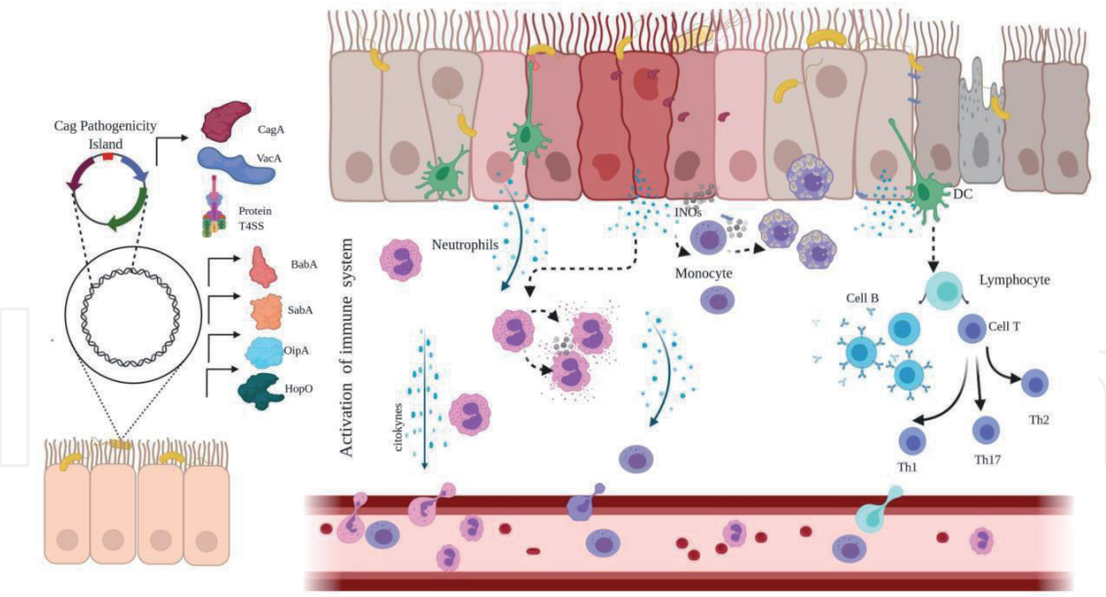

Figure 1.
Infection of Helicobacter pylori *activates immunity system.* Helicobacter pylori *(*H. pylori*) has different virulence factors which contribute to the activation of the immune system. CagA and VacA are proteins coded by the pathogenic island to induce the secretion of inflammatory cytokines in the gastric epithelium, which attracts neutrophils and monocytes to the infection site. The activation of these cells causes inflammatory conditions by triggering their effector mechanisms such as degranulation and ROS production. Subsequently, DC processes and present the antigen which induces a specific response through the lymphocyte.*

change the expression of CagA; for example, pH 6.0 induces higher expression of CagA when compared with pH 7.0, even at a pH 4.0, it increased the expression of CagA but decreased the survival of *H. pylori,* especially strains with a high number of EPIYA repeat regions [1].

A high-salt diet modifies the expression of the CagA protein and transcriptome level in *H. pylori* [10]. In a gerbils infection model, a high-salt diet induced higher *cagA* expression compared with *H. pylori*-infected gerbils with a regular diet; however, the first group had higher levels of inflammatory cytokines (IL-1, IL-6, IL-17, and gamma interferon [IFN-γ]), anti-inflammatory cytokines (IL-10), chemokines (KC, CCL12), and inducible nitric oxide synthase (iNOS); in consequence, there were higher inflammation scores as well as a higher frequency of gastric carcinoma [11].

Using an animal model, Noto *et al*., 2013, demonstrated that gerbil iron-depleted diets and infected with CagA positive strains enhanced virulence and induced robust proinflammatory responses. All of these things induce premalignant and malignant lesions; lower levels of iron are a risk factor for gastric cancer [12].

2.1.2 VacA

VacA is a pore-forming cytotoxin that plays a role interacting with gastric cells, induces vacuole formation, and apoptosis in mammalian cells; it is a pro-toxin of 140 kDa that is secreted through the auto-transporter pathway. The mature protein 88 kDa secreted toxin undergoes proteolysis in two fragments: p33 and p55 [3]. The *vacA* gene is not part of cagPAI; it has three polymorphic regions: the signal (s) intermediate (i) and middle (m) regions [13]. The s-region of *vacA* is divided into s1 (s1a, s1b, and s1c) and s2 genotypes. The m-region, which is composed of about 300 amino acids, is classified into m1 (m1a and m1b) and m2 genotypes; there is a segment located in the middle region of the 148 amino acid that exploits the cell binding specificity of VacA and plays a in a better survival for *H. pylori* inside the

gastric epithelial cells [3]. The i-region is located between the s- and m-regions of *vacA* and it is composed of different combinations of 3 clusters (A, B, and C). The i-region is classified into the i1 and i2 genotypes, according to the combination of clusters that are present [3].

The studies have revealed that the combination of different sequences in the three regions can determine the capability of vacuolation. *s*1-type VacA has been suggested to be associated with peptic ulcers, *m*1-type VacA induces vacuolation in HeLa cells, and strains with the *i*1 genotype are strongly associated with gastric cancer and vacuolating cytotoxin activity [13]. There are western strains that have a deletion (*d*) region located between the *i* and the m regions, the *d* region can be *d*1 or *d*2.

VacA is a risk factor for gastric mucosal atrophy. All s1/i1/d1 strains are called East Asia *Helicobacter* type [2]. Do Carmo *et al*., 2011, demonstrated that only the presence of *vacA* s1 and the absence of *cagA* have a major role in the development of gastric cancer [14].

The secretion inside the VacA cell induces the production of antibodies against VacA; however, there is a meta-analysis in which an association of VacA antibody with peptic ulcer disease and gastric cancer risk is observed; furthermore, the higher level of antibody response to VacA is associated with a risk of extra-gastric disease, such as colorectal cancer in African Americans [3].

Another target of VacA inside the cells is the endoplasmic reticulum; it produces stress and activates autophagy and increased cellular death. VacA is very important to survival efficacy through a transient receptor potential membrane channel mucolopin 1 (TRPML1) activity that inhibits the lysosomal and autophagy killing of bacterial cells to promote the establishment of an intracellular niche that allows bacterial survival, in addition to an altered host immune response, mainly through the inhibition of T cell activation and proliferation (**Figure 1**) [2].

2.1.3 Outer membrane proteins and gastric cancer

The outer membrane is the outer barrier of Gram-negative bacteria that contains outer membrane proteins (OMPs) resistant to the external environment. The OMPs have a variety of biological functions, such as maintaining the outer membrane structure and guaranteeing the material transportation especially, the OMPs participate in the adherence of *H. pylori* to the gastric mucosa, they play important roles in the initial colonization and long-term persistence on the gastric mucosa, as well as in the intensity of the resulting inflammatory response [14, 15]. OMPs in *H. pylori* mainly include lipoproteins, porins, iron-regulated proteins, efflux pump proteins, and adhesins. 4% of the whole-genoma encode OMPs; the expression of OMPs is variable and depends on geographical differences, being the five best characterized: BabA (HopS), SabA (HopP), OipA (HopH), HopQ and HopZ [15].

2.1.3.1 BabA (HopS)

Blood group antigen-binding adhesin (babA) is a 78-kDa outer membrane protein encoded by the babA2 gene, which binds the fucosylated Lewis b antigen (Le^b) on the surfaces of gastric epithelial cells. The specific manner by hydrogen bonds network structure formed between four residues of Lewis b and eight amino acids of BabA. *H. pylori* has blood group binding preferences; some strains combine only with O antigen residues. Persons with type O blood are more likely to suffer peptic ulcer than those with other blood types for it overexpresses Lewis b [16]. A special study demonstrated that the expression of BabA is acid-sensitive and has nothing to do with the binding affinity of Lewis b [17]. However, the expression loss of BabA is

not related to adaptive immunity or the Toll-like receptors (TLRs) [18]. The protein encoded for three genomic loci has been found in *bab*, namely, *babA*, *babB,* and *babC*; from these, only the babA2 is functional for binding activity. Almost 18,000 strains have two babA alleles, which are babA1 (silence) and babA2 (expression) [15]. In patients from Saudi Arabia, *H. pylori* was isolated and PCR were performed; the *babA2* gene strains were associated with a high risk of gastric cancer and a strong relation with VacAs1 and the prevalence of these genotype were higher. The strains of *H. pylori* carrying *babA2*, *cagA*, and *vacAs1* genotypes were associated with the risk of intestinal cancer [19].

2.1.3.2 Sialic acid-binding adhesin (SabA)

SabA binds to gangliosides with fucose substitutions of the N-acetyllactosamine like the dimeric sialyl-Lex antigen [3]. SabA is the second most commonly reported adhesin in *H. pylori,* also known as HopP or OMP17. The *sab* gene has two alleles, sabA and sabB [15]; however, *H. pylori* selectively expresses SabA during the colonization. This is caused by slipped-strand mispairing in 5'dinucleotide repeat region, which affects the on–off states of *sabA* and *sabB* [15]. This state reflects the ability of *H. pylori* to adapt to the host. The acid-responsive signaling, such as the environment pH activates the signal transductions to *H. pylori* to expresse SabA. *H. pylori* alters the gastric mucosa glycosylation and up regulates the sialyl-Lex antigens, promoting the attachment of SabA to the gastric mucosa. The SabA binding produces inflammation and allows bacterial persistence and gastric pathogenicity establishment. Several studies have reported an association between SabA expression and an increased risk of chronic gastritis, intestinal metaplasia, corpus atrophy, and even gastric cancer. The construction of a profile with the combination of SabA with other virulence factors, such as OipA and BabA, can be used as a prognostic marker, for it could distinguish the patients with gastric cancer from duodenal cancer patients and healthy individuals [3]. However, the only presence of SabA related with gastric cancer risk was showed in a Japanese population [20]. Nevertheless, another study showed that SabA-positive strains were no related with gastric cancer [21].

2.1.3.3 OipA

The outer inflammatory protein A (OipA), also called HopH, *oip* gene, is approximately 100 kb from the cagPAI, and usually CagA positive strains have OipA expressed. OipA is a protein with a molecular weight of 34 kDa; it can increase the secretion of interleukin-8 (IL-8) to cause neutrophil infiltration that produces inflammatory environment, which helps *H. pylori* colonization. However, OipA can induce inflammation and affect actin dynamics through the phosphorylation of multiple signaling pathways that usually interact with cagPAI-related pathway. Therefore, OipA inhibits the apoptosis of gastric cells and has a role in the activation of focal adhesion kinase (FAK), which is a cytoplasmic non-receptor tyrosine kinase and can regulate the shape of the cells, cell movement, and this is an essential role in the occurrence and invasive growth of tumors [22]. The Asian and Western strains that have expressed OipA are correlated with peptic ulcer, gastric cancer, and MALT. The signaling pathway related to carcinogenesis is regulated by the activation of the phosphoinositide-3 kinase (PI3K)/Akt, and, at the same time, the same signaling pathway regulates IL-8 secretion through forehead transcription factors of class O (FoxO) 1/3a inactivation.

In an animal model, mice were inoculated with immunogenic OipA and *H. pylori* at the same time and showed that the colonization and inflammation were

reduced [23]. Maybe the OipA vaccine is a therapeutic target to the *H. pylori* infection and could prevent the development of gastric cancer. On the other hand, the inactivation of OipA produced a decreased level of nuclear β-catenin *in vitro* and a reduced incidence of cancer in gerbils; OipA is very important in the *H. pylori* infection [24].

2.1.3.4 HopQ

Another OMP that plays an important role in the initial colonization is the *hopQ* gene; it is present in 2 forms: type I and type II. The presence of type I *hopQ* alleles and another *H. pylori* virulence markers, including type s1 *vacA* alleles, *hopQ* are essential for CagA translocation and transformation of the hummingbird phenotype and cell scattering, for the targets are β-strands. G, F, and C in the N-terminal domain (C1ND) and the IgV-like domain of carcinoembryonic antigen-related cell adhesion molecule family (CEACAMs), mainly CEACAM1, CEACAM3, CEACAM5 and CEACAM6, and the interaction of HopQ-CEACAM interaction facilitates the transference of CagA to the host cells and induces signal transduction [15]. The suppression or deletion of *hopQ* reduces T4SS-dependent activation of NF-κB, induction of MAPK signaling and the secretion of IL-8 in the host cells, but it does not affect the attachment of the bacteria to the host cells. Patients with hopQ type I strains have more inflammatory cell infiltration and atrophy than those with hopQ type II strains [24].

So far, we already know which virulence factor helps Helicobacter to colonize and persistent in the stomach, but what happens with the immune response of the host and their genetic susceptibility?

2.2 Host characteristics

2.2.1 Genetic susceptibility

Host genetic susceptibility depends on polymorphisms of genes involved in *H. pylori*-related inflammation and the response of cytokines in gastric epithelial and immune cells. *H. pylori* strains differ in their ability to induce a deleterious inflammatory response. *H. pylori*-driven cytokines accelerate the inflammatory response and promote malignancy by DNA damage, the impairment of repair processes, and increase the rate of mutation [25].

The receptor which recognizes multiples virulence factor of *H. pylori* or of any microorganism are the Toll-like receptors (TLR's). These receptors are present in the surface and inside of the intracellular vesicle of any mammalian cell, but mainly in immunological cells, such as macrophages, neutrophils, T cells, and B cells.

Groups of receptors are simultaneously engaged in the recognition of *H. pylori* compounds and the development of gastric cancer; these are TLR2, TLR3, TLR4, TLR5, and TLR9 (**Figure 2**) [25].

It has been shown that *H. pylori* LPS, as the TLR2 ligand, induces the secretion of chemokines by gastric epithelial cells; however, TLR4 also recognizes LPS [25]. *Moran AP. 2001*, proposed that *H. pylori* LPS reduced immunogenicity by uncommon phosphorylation and acylation of *H. pylori* lipid A [26]. Another work showed *H. pylori* LPS has anti-phagocytic properties *in vitro* [27].

Chochi *et al*. 2008, showed that TLR4 increased the growth of gastric cancer [28]. There are studies that showed that single nucleotide polymorphisms (SNPs) of TLR2 and TLR4 receptors were associated with an increased risk of gastric carcinoma in some population [29].

Metanalysis of TLR2–196 to –174 showed in a Japanese population that this deletion decreased the induction of IL-8 and is associated with a risk of gastric cancer

compared with controls group [29], but this correlation failed in a Chinese population; this may indicate an ethnic consideration in the incidence of stomach cancer.

Single nucleotide polymorphisms (SNPs) of the TLR4 receptor were associated with an increased cell death against *H. pylori*, whose effectiveness affects the risk of gastric carcinoma, including TLR4 rs4986790 (Asp299Gly), TLR4 rs4986791 (Thr399Ile), TLR4 rs10116253, TLR4 rs10983755, TLR4 rs11536889 (C3725G/C), TLR4 rs1927911. TLR4 Asp299Gly and Thr399Ile polymorphisms generate less stability of the extracellular domain [30]. In an Iranian population, the TLR4 (Asp299Gly) G and DG *alleles* were associated with chronic active gastritis [31]; in a Western population, the G allele as well as the TLR4 rs11536889 C allele and the CC genotype increased the risk of gastric cancer [32]. Different associations were obtained with the polymorphisms, for it depends of the genetic background of the population; therefore, the risks of cancer or inflammatory gastric disease totally depend on ethnicity.

The second part of the activation of the pattern recognition receptors on the leukocyte and epithelial/endothelial cells induce the production of cytokines. All these elements are part of the inflammatory environment, they could regulate tumor growth and metastasis, cause discomfort symptoms, and potentially influence the tumor prognosis [33].

Another pathogenic factor of *H. pylori* is flagellin; its principal role is motility and colonization. The flagellin is made of two separate subunits, FlaA and FlaB and it is recognized by TLR5 [34], Andersen-Nissen *et al.,* 2005 showed that dimer TLR5-flagellin failed to induce the nuclear factor (NF)-kB activation, allowing the evasion of the immune response (**Figure 2**) [35].

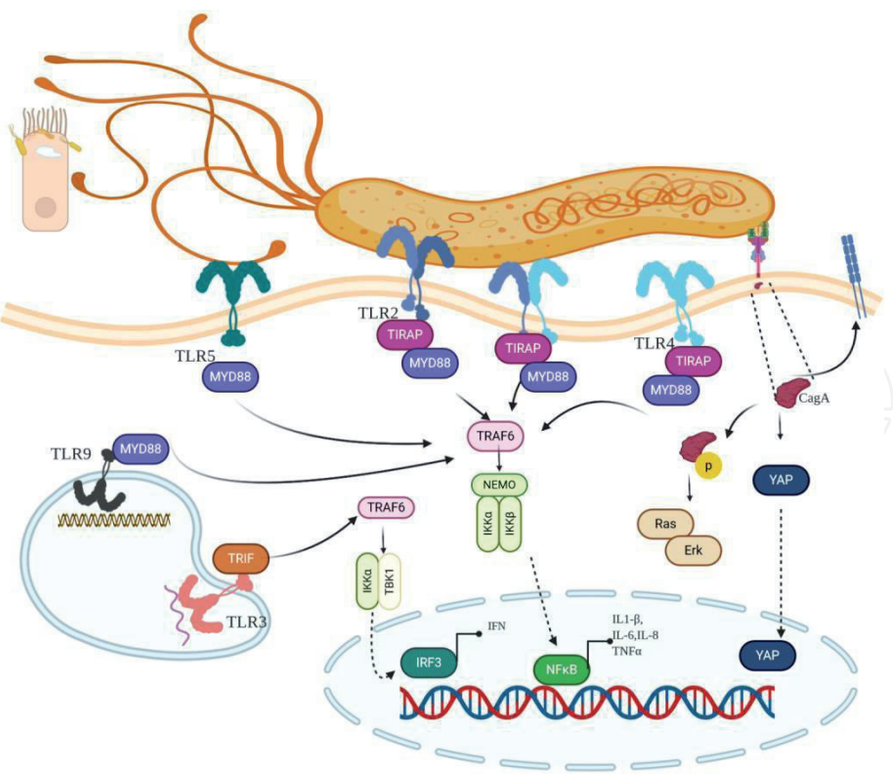

Figure 2.
Signaling of TLRs activate for Helicobacter pylori. *Toll-like receptors (TLRs) are pattern recognition receptors which distinguish conserved microbial products of* H. pylori. *TLR2, TLR4, TLR5 and TLR9 are expressed over the cell membrane. TLR3 and TLR9 are expressed over the endosome. All TLRs expected for the TLR3 activate MyD88-dependent pathway to induce NF-κB and p38/JNK to activate AP1, to induce the production of proinflammatory cytokines. However, TLR3 requires IRIF to activate the production of IFNα/β. additionally,* H. pylori *infection induces YAP and downstream effects over the gastric epithelial cell.*

After the activation of immune and epithelial cells, there is a production and secretion of pro-inflammatory and anti-inflammatory cytokines such as tumor necrosis factor (TNF-α), IL-1β, IL-8, and IL-10 [25], which leads to the recruitment of macrophages, neutrophils, and lymphocytes to the gastric tissue [36].

H. pylori has a different mechanism to evade the immune response, some examples are; VacA alters the antigen presentation by B cells, VacA affects endosomal traffic, preventing the development of the TH1 response. *H. pylori* affects the host's trafficking pathways, it produces modifications in GTPases in macrophages, and deletes the expression of *Rgs1/2, Fgd2* and *Dock8,* which are regulators of Rho, Pac, and Cdc42 GTPases, respectively. This disrupts the actin cytoskeleton and phagocyte function [36].

H. pylori can inhibit the killing by reactive oxygen species and nitric oxide for it disrupts NADPH oxidase. On the other hand, *H. pylori* activates the inducible iNOS in macrophages by urease and the arginase, which produces less amount of oxide nitric.

Once the infection starts, dendritic cells are the first cells to arrive to the gastric mucosa and produce IL-6, IL-1β, IL-12, and TNF-α, which causes inflammation and Th1 response. During atrophic gastritis, the macrophages are polarized to M1 subtype and induce proliferation of T cells; however, *H. pylori* can stimulate M2 macrophages. In consequence, there are less inflammatory cytokines and the immune response is balanced (**Figure 3**) [37, 38].

In contrast, *H. pylori* activates the ERk1/2 pathway and then the activation of the AP-1 complex. This complex generates an increased expression of ornithine decarboxylase that induces apoptosis in macrophages [36]. Another mechanism of *H. pylori* that induces apoptosis is through the Fas pathway using the HP986 protein [39]. The last mechanism to induce monocyte apoptosis is through the p52 fragment of VacA, which activates NF-κB pathways and induces proinflammatory cytokines such as TNF-α, IL-1β, NOS, and ROS, subsequently causing apoptosis.

In dendritic cells (DC), VacA causes a decreased expression of CD40, CD80, CD86, MHC class II, and decreases the secretion of IL-1β, IL12p70 and TNF-α; the major effect of the down expression is the inhibition of the T cell response [40].

Patients infected with *H. pylori* showed an increase of CD4+ CD25 T cells (Treg); these cells allow an increase of bacterial load and induce chronic infection by suppressing the immune response; additionally, the Treg induces the secretion of TGF-β and IL-10 [36]. *H. pylori* can up-regulate the expression of B7-H1 and, at the same time, down regulate the B7-H2 expression on epithelial gastric cells; this change can induce alterations of the T cell subpopulation, increasing Treg and decreasing Th17 [41].

There is some evidence that virulence factors such as VacA and CagA cause damage in gastric cells and result in peptic ulcer, even gastric cancer. Now we know that the severity of gastric diseases depends on the virulence factor together with the host factor.

2.2.2 Immune factors

Immune dysregulation plays a pathogenic role in the development of cancer.

Colonization of *H. pylori* induces acute inflammation; this response is highly reactive but it is unable to eradicate the infection. If with time the infection persists, the inflammation will be regulated and is considered a chronic inflammation.

Chronic inflammation of the gastric mucosa evolves in three forms: (1) antral-predominant, (2) corpus-predominant, and (3) diffuse [25]. Antral-predominant gastritis promotes duodenal ulcers whereas corpus-predominant gastritis promotes gastric ulcers [25].

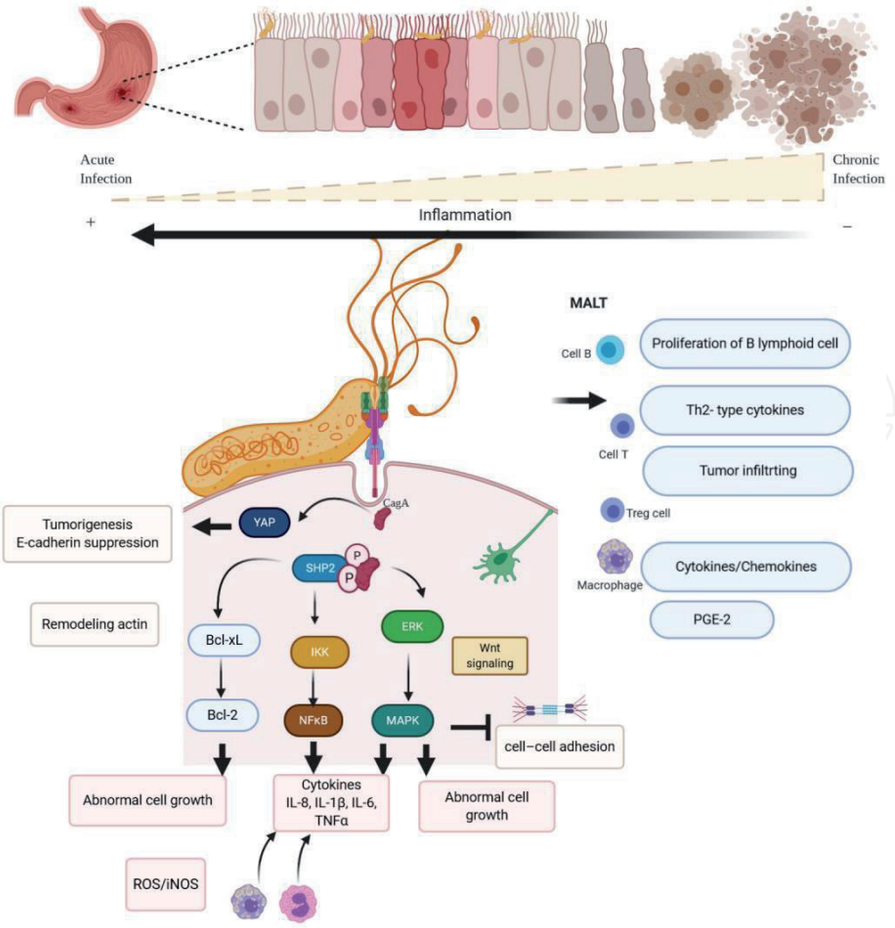

Figure 3.
Role of Helicobacter pylori *in peptic ulcer and gastric cancer.* H. pylori *Infection modulates a variety of host cell signal pathways and the crosstalk of MAPk, ERK, WNT, and YAP pathways.* Helicobacter pylori *colonizes the gastric mucosa in the human stomach and represents a major risk factor for peptic ulcer disease and gastric cancer.* H. pylori *Manipulates host signal networks, to trough, by the cag pathogenicity island (cagPAI)-encoded type IV secretion system (T4SS).* H. pylori *Infection includes the disruption of cell–cell junctions and cytoskeletal rearrangements, as well as proinflammatory, cell cycle-related, proliferative, antiapoptotic, and DNA damage responses and epithelial mesenchymal transition (EMT).*

In atrophic gastritis, the principal and parietal cells are replaced by globlet cells as the lesion progresses giving way to intestinal cancer; this transformation is called metaplasia. In general, there are two different types of metaplasia, intestinal metaplasia and spasmolytic polypeptide-expressing metaplasia (SPEM); both types of metaplasia are associated with the progression of intestinal-type gastric cancer.

In intestinal metaplasia, globet cells express intestinal markers such as Muc2 and Trefoil factor 3 (TFF3) [42].

In spasmolytic polypeptide-expressing metaplasia (SPEM), the cells have a morphological characteristic more typical of deep antral gland cells or Brunner's glands, expressing Muc6 and Trefoil factor 2 (TFF2).

The type II cytokines, including IL-4, IL-5, and IL-9, can activate type II innate lymphoid cells (ILC2). These lymphocytes respond to IL-33 producing IL-13 [43].

The development of metaplasia involves alarming cytokines, such as IL-33 and IL-13. IL-13 induces chief cell trans differentiation into SPEM, following the loss of parietal cells from the corpus of the stomach, and activated macrophages, which promotes the resolution of inflammation and wound repair [44]. Subsequently, it drives the progression of metaplasia to become more proliferative with increased intestinal characteristics; furthermore, SPEM is a phenotype in the atrophic gastritis and correlates with intestinal-type gastric cancer [43].

In general, gastric cancer shows an immunosuppressive character. There are tumor-infiltrating leukocytes, such as CD8+ T cells, CD68+ macrophages, and CD4+ T cells, that represent 15%, 13%, and 11% of all intratumorally cells, respectively. The role of the immune response has a strong selective pressure on the tumor and allows its growth; finally, it helps the cancer-immunoediting process, one of the mechanisms to demonstrate it is the down expression of PD1/PDL1. This response induces pro-tumoral effects such as angiogenesis and metastasis [45]. In our experience, the immune response can be a diagnostic marker to gastric cancer independently of the histological subtype (**Figure 3**) [33].

2.3 Environmental factors

2.3.1 Dietary factors

The dietary factors that have an important impact on gastric cancer are low intake of fresh fruits and vegetables, high-sodium diet, salt-preserved food, red and cured meat; all these are associated with gastric cancer risk.

2.3.2 Other

High alcohol intake, tobacco smoking, and high weight were associated with gastric cancer risk in a prospective study in a studied cohort, demonstrating that 62% of cardia gastric cancer could have been prevented if the population had followed a healthy lifestyle [46]. The primary prevention of gastric cancer includes healthy diet, anti-*H. pylori* therapies, and screening for early detection [47].

2.4 Development of gastric cancer

Gastric cancer is a carcinoma that occurs sporadically most of the times. It is associated to *H. pylori* infection and is commonly caused by coincidence with many risk factors. There is a geographical variation in cancer gastric variation, 70% the of cases occurs in developing countries and half of the total case occurs in Eastern Asia, especially China. This country has the highest mortality rates, and the highest mortality rates in Central and Eastern Europe, Central and South America, whereas the lowest rates occur in North America [48].

Most gastric cancers are diagnosed at an advanced stage; 25–50% of the cases will develop metastasis. The main treatment with curative-intent in gastric cancer patients is surgery, being associated with approximately a 5-years survival rate of 20–25%; therefore, additional treatments are chemotherapy and radiotherapy but unfortunately they lead only to a modest survival benefit [43].

In 1965, Lauren described two histologically different stomach adenocarcinomas, diffuse and intestinal. The diffuse type is considered an endemic cancer type.

Diffuse adenocarcinoma affects mostly women and younger populations. The intestinal type is related to preneoplastic changes, such as chronic atrophic gastritis and intestinal metaplasia of mucous membranes. This type causes tumors in the peripheral part of the stomach. Intestinal adenocarcinoma is an epidemic type of cancer for it occurs in regions with a high risk of gastric cancer morbidity. It affects mostly men and older populations [36, 45].

The ratio of intestinal and diffuse types varies among countries. For example, intestinal type is more common and occurs more often in the distal stomach, in high-risk area and it is often preceded by long-standing precancerous lesion in European countries.

Another classification was proposed by the Word Health Organization (WHO). There are four histological subtypes: papillary, tubular, mucinous and poorly cohesive. Both classifications are inadequate, for they stratify patients regarding tumor behavior, prognosis, and response to specific treatment.

There is also the molecular classification in which gastric cancer is divided into four genomic subtypes: Chromosomal instability, Microsatellite instability, Genomic stability, and Epstein Barr virus-associated [49].

Chromosomal instability is associated with loss or gain of tumor suppressor genes, such as TP53, and receptor tyrosine kinase mutation that affects the cell cycle gene and MET, RAS, BRAF, HER2, and EGFR; the tumors are located at the gastroesophageal junction [49].

Microsatellite instability is associated with abnormal absences of the protein expression and it is diagnosed by immunohistochemistry or polymerase chain reaction (PCR); the sensitivity of the test is between 83 and 89% and the specificity is 89–90% [50].

Genomic stability: in diffuse gastric cancer the main somatic genomic alterations are CDH1, ARIDIA and RHOA, and they are involved in cellular motility [48].

Epstein Barr virus-associated: 10% of gastric cancer patients have been detected with Epstein bar virus, especially in far East Asian patients and it is more frequent in younger persons [48].

Development of gastric cancer associated to *H. pylori* strains carrying the cagPAI, induces the NF-kB transcription factor, and CagA and VacA are dispensable for direct NF-kB activation. NF-kB-driven gene products include cytokines/chemokines, growth factors, anti-apoptotic factors, angiogenic regulators, and metalloproteinases. Many of the genes are transcribed by NF-kB promote gastric carcinogenesis. All of the pro-inflammatory mediators lead the accumulation of genetic and epigenetic changes in differentiated and steam cells. Chronic inflammation is the initial step towards atrophy, metaplasia, and dysplasia and a promoter of cancer development [51]. Furthermore, the recruitment and activation of inflammatory cells, genetic predisposition, the activation of the cells with the environmental factors, and more pathogenic strains induce the progression and metastasis of gastric cancer.

3. Conclusion

Cancer gastric is a multifactorial cancer and many factors can play a role in its incidence. In the present review, several *H. pylori* pathogenic factors, environmental factors, genetic susceptibility, and immune factor in the host were described in the contributing role in the development of cancer gastric.

Different histological types of gastric cancer and anatomic location might suggest different etiologies of gastric cancer; however, genetic predisposition and inflammatory response have a consequence in a process regulating proliferation, evasion of apoptotic development of synergistic complex for the development gastric cancer, and, eventually, metastasis.

It is necessary to know the different risk factors involved in the development of gastric cancer in order to implement better therapies and a better prognosis for patients.

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Conflict of interest

"The authors declare no conflict of interest."

Abbreviations

ARID1A	AT-richnteractive domain-containig protein 1 A
BabA	Blood group antigen-binding adhesin
BRAF	Serine–threonine kinase
CDH1	gene coding E-cadherine
C1ND	C in the N-terminal domain
cag PAI	cag Pathogenicity Island
CEACAMs	Carcinoembryonic antigen-related cell adhesion molecules
DC	Dendritic cells
EGRF	Epidermal growth factor receptor
FAK	Focal adhesion kinase
FoxO	transcription factors of class O
HER2	Human epidermal growth factor receptor
IFN-γ	Gamma interferon
IL	Interleukin
ILC	Innate lymphoid cells
iNOS	inducible nitric oxide synthase
Leb	Lewis b antigen
MET	Receptor tyrosine kinase
NF-κB	Nuclear factor kappa B
OipA	Outer inflammatory protein A
OMPs	Outer membrane proteins
PCR	Polymerase chain reaction
PD1/PD-L1	Programmed death 1/ligands *PD-L1*
PI3K	Phosphoinositide-3 kinase
RHOA	Ras homolog family member A
SHP2	Src homology 2 phosphatases
SNPs	Single nucleotide polymorphisms
SPEM	Spasmolytic polypeptide-expressing metaplasia
T4SS	Type IV secretion system
TFF2	Trefoil factor 2
TFF3	Trefoil factor 3
TLRs	Toll-like receptors
TRPML1	Transient receptor potential membrane channel mucolopin

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