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A Double-Edged Sword: Roles of Helicobacter Pylori in Gastric Carcinoma

Li-Jun Xue [1], Quan-Sheng Su[1], Xiao-Bei Mao[1], Qing Lin[1], Xiao-Bei Liu[1], Chang Liu[2], Yong Lin[1], Ji-Hong Yang[1], Hong-Ju Yu[1] and Xiao-Yuan Chu[1]

[1]*Departments of Oncology and*
[2]*Gastroenterology, Jinling Hospital, Nanjing University School of Medicine, 305 East Zhong-shan Road, Nanjing, Jiangsu Province, China*

1. Introduction

Gastric carcinoma (GC) remains one of the most malignant tumors either in morbidity or mortality rates around the world (IARC, 2002). Development of GC is influenced by multiple factors including genetic, biological, social, and psychological ones, etc.., however, the function mechanisms of which are too sophisticated and still under explorations (Matysiak-Budnik & Mégraud, 2006). Similar to other malignant tumors, GC leads to death mainly due to system or organ failure because of cancer advancement and metastasis. Chemotherapy-based regimens combined with radiological and immunomodulating therapies are fundamental but unsatisfactory because most GC patients are in advanced stage when diagnosed, although radical operation throws those at early stage a light of prolonged survival and even clinical cure (Quiros & Bui, 2009). As for prophylaxis, many reports have mentioned the protective role of eradication of *Helicobacter pylori*, which has been identified as a definite carcinogen for GC, but few evidences proved a successful *H. pylori* vaccine showing effects on GC prevention, just as Hepatitis B virus vaccine on prevention of primary hepatocellular carcinoma (IARC, 1994; Murakami et al., 2005; Cai et al., 2005; Di Bisceglie 2009).

H. pylori, a stomach colonizing spiral gram-negative bacterium, interacts with the host in a multiplicity of ways during its adhesion, colonization, invasion, and induction of inflammatory and immune responses (Peek 2005). The great majority of researchers link *H. pylori* infection with development or even recurrence of GC according to some clinical trials, meta-analyses, and *in vitro* experiments (Wong et al., 2004; Fukase et al., 2008). However, a few recent studies have disclosed the other side of the coin, in which positive *H. pylori* status appears to be associated with better outlook in GC patients (Meimarakis et al., 2006; Marrelli et al., 2009). Therefore, *H. pylori* probably factually play a bi-directional role in GC just like a double-edged sword. To learn about both edges of *H. pylori* infection will provides us with new sights in vaccine design, prevention, and even therapy of GC.

Herein, we try to re-elucidate the relationship between *H. pylori* and GC from novel angles, in which GC consists of *H. pylori*-related (Hp-GC) and non-*H. pylori*-related (nHp-GC) ones,

and in which roles of the infection are divided into two parts including harmful and beneficial ones.

2. H. pylori virulence factors

H. pylori infection usually initiates from bacterial invasion, colonization, and expression and translocation of virulence factors, and persists through induction and maintenance of complex responses at certain levels in the host (Peek 2005). Herein, virulence factors extensively mean pathogenic components and contain those contributing to bacterial survival within the host, which are ever called as maintenance factors sometimes. According to the complete genome published and continuously updated since 1997, *H. pylori* (26695 strain) is of about 1.67 Mb in length with 1576 protein-coding genes, many of which encode virulent products associated with *H. pylori* pathogenesis (Tomb et al., 1997).

The cytotoxin-associated gene (cag) pathogenicity island (PAI), one of most well known virulence components, is of about 35 Kb with 26 open reading frames and is present in about 60% *H. pylori* strains in Europe and United States (Tomb et al., 1997; Peek 2005). Among all Cag PAI products, the CagA (Cag26) has been identified with relatively clear functions in development of GC (Huang et al., 2003). The involved carcinogenic mechanisms of CagA mainly include activation of certain signalling pathways such as Ras, SHP2, ERK, MAPK and JAK/STAT3, activation of C-terminal Src kinase and inhibition of Src activity, enhancement of epithelial gene transcription, disruption of cellular polarity, and morphological changes and final transformation of gastric epithelial cells (GECs) (Mimuro et al., 2002; Higashi et al., 2002; Selbach et al., 2002; Bagnoli et al., 2005; Lee et al., 2010).

Vacuolating toxin (vacA) of about 3.9 Kb is an independent key virulence determinant for *H. pylori* pathogenesis (Tomb et al., 1997). Around 60% of *H. pylori* strains produce detectable amounts of VacA *in vitro*, although this gene is present in all strains (Konturek et al., 2009). Cytotoxic activity of VacA varys considerably in different strains due to various gene subtypes based on sequence diversities in the N-terminal (allele types s1a, s1b, s1c, or s2) and middle regions (allele types m1 or m2) (Atherton et al., 1995; Peek 2005). It has been demonstrated that infection with vacA s1 and m1 strains are associated with an increased risk of GC (Gerhard et al., 1999). VacA plays a role in carcinogenesis probably through inducing vacuolation and cellular detachment, permeabilizing epithelial cells, promoting apoptosis, and suppressing T-cell proliferation and activation (Peek 2005).

Outer membrane proteins (OMP) represent a large family of adhesins and participate in *H. pylori* infection mainly by mediating bacterial adherence and colonization in gastric mucosa (Odenbreit 2005). As one of OMP members, blood-group antigen-binding adhesin (BabA) can bind the blood-group antigen Lewis b on host epithelial cell membranes, and those strains possessing the encoding gene babA2 are associated with high risk of GC (Oliveira et al., 2003; Konturek et al., 2009). Lipopolysaccharide (LPS), another cell wall component, can disrupt stomach mucosa and involve in the organism survival and persistence of *H. pylori* infection (Grebowska et al., 2008). Moreover, the LPS O-antigen mimics human Lewisx and Lewisy blood-group antigens, which also mediate bacterial adhesion and colonization and alternatively cause immune cross-reactivity (Moran 1996; Appelmelk et al., 2001).

There are still many other important virulence factors related with *H. pylori* infection and even carcinogenesis. Urease, an approximately 560-kDa hexameric enzyme consisting of 30-kDa UreA and 64-kDa UreB subunits, is produced abundantly by all *H. pylori* isolates (Turbett et al., 1992). Urease is independently essential for colonization and persistent

survival of the germ because it crucially contributes to local pH homeostasis within the stomach lumen (Stingl et al., 2002; Mollenhauer-Rektorschek et al., 2002). The induced by contact with epithelium factor Antigen (IceA), with two major allelic sequence variants of IceA1 and IceA2, is an independent strain-specific *H. pylori* locus significantly associated with distal GC (Kidd et al., 2001). IceA1 leads to relatively severer gastric inflammation and tissue damage following production induced by bacterial contact with GECs, which exists in 72% of the *H. pylori* isolates in a Chinese population (Sheu et al., 2002). Flagella are bacterial motile structures with two types of filaments, that are encoded by flaA and flaB genes and functionaly regulated by flgE and flbA genes (Dunn et al., 1997). Normal expression and interaction of these virulence factors are required for bacterial motility or colonization during *H. pylori* infection.

Notably, *H. pylori* plays pathogenic or carcinogenic roles as an integrity, although its multiple virulence components have their own special contributions at various infection stages. The co-interactions among the virulence factors are likewise important for pathogenesis but may be so complex or always ignored and need further explorations. In addition, cross-interactions between *H. pylori* and the host are very vital for infection or carcinogenesis, which mainly contain inflammatory and immune responses, and genetic or phenotypic alterations (McNamara & El-Omar, 2008).

3. Inflammatory responses

H. pylori infection is firstly characterized by acute or chronic activation of inflammatory cells and release of multiple cytokines including pro-inflammatory and inflammatory ones (Peek 2005). The spectrum and relative levels of cytokines, to a certain extent, reflect the intensity of the host response to infection, which may result in different outcomes including gastric mucosal inflammation, injury, ulcer, and even cancer.

Cytokines such as tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β) / IL-1 receptor antagonist (IL-1RN), IL-6, IL-8 and IL-10 are always significantly up-regulated in stomach mucosa, gastric fluids and the sera of *H. pylori*-infected patients and play vital functions in gastritis, metaplasia, dysplasia and carcinogenesis (McNamara & El-Omar, 2008). TNF-α and IL-1 are the most relevant factors consistently confirmed in animal models and various populations. TNF-α can markedly potentiate apoptosis, activate signalling pathways, influence mucosal inflammation and stimulate gastric acid secretion (Ierardi et al., 2003). Moreover, *H. pylori* causes sensitization of GECs for TNF-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis, besides direct induction of apoptosis and inhibition of DNA synthesis (Tsai & Hsu, 2010). The *H. pylori* infection strengthens IL-1 functions in the carcinogenic process through complex pathways. IL-1β and IL-1RN as key pro-inflammatory genotypes of IL-1, which is a powerful gastric acid suppressor, can increase the risk of atrophic gastritis (AG) and both intestinal and diffuse types of non-cardia GC (Starzyńska et al., 2006; Rad et al., 2004). IL-1β with significantly higher level in neoplasm than in normal mucosa, involves in the carcinogenesis by stimulating hyper-proliferation in GECs via tyrosine kinase signalling (Beales 2002). *H. pylori*-induced gastritis is possibly driven in an IL-6-dependent fashion (Jackson et al., 2006). IL-6 participates in activation of the STAT3 signalling pathway by the translocated CagA in host cells, which may play a role in gastric carcinogenesis (Bronte-Tinkew et al., 2009). IL-6 level in the serum is related with GC status and its level in the tumor correlates significantly with lymphatic invasion and the depth of invasion (Kai et al., 2005). As for IL-8, its level in cancer tissues is more than double

fold in advanced GC than that in early GC irrespective of *H. pylori* status (Yamaoka et al., 2001). IL-8 modulates gastric acid secretion, promotes the proliferation, enhances the FasL-induced apoptosis, and mutually and dependently activates NF-κB (Konturek et al., 2002; Varro et al., 2004; Guo et al., 2006). Moreover, IL-8 as a potent leukocyte chemoattractant, contributes to mucosal tissue injury and induces the upregulation and phosphorylation of EGFR and subsequent signalling events, which plays an fundamental role in carcinogenic mechanisms (Kassai et al., 1999; Beswick & Reyes, 2008). IL-10 inhibits the FasL-induced apoptosis in GECs though without significant effect on the transcription of Fas (Guo et al., 2006). IL-11 activates the STAT3 like IL-6 and concomitantly increases proliferation of GECs (Jackson et al., 2007).

Some other molecules including cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), nitric oxide (NO), inducible NO synthase (iNOS), monocyte chemoattractant protein 1 (MCP1), and hepatocyte growth factor (HGF) and c-MET also relate to GC-associated inflammatory responses (Zhuang X et al., 2001; Futagami et al., 2008; Snider & Cardelli, 2009; Cho et al., 2010). COX-2 as a key mediator in inflammation and cancer formation, together with PGE2, one of its major products, are remarkably up-regulated in *H. pylori*-related gastritis, GC, and precancerous lesions including atrophy, intestinal metaplasia (IM) and dysplasia of the stomach (Dong et al., 2009; Walduck et al., 2009; Zhang et al., 2009). COX-2 can be induced by gastrin, growth factors, inflammatory cytokines and reactive oxygen species in GECs (Seo et al., 2007). The overexpression of COX-2 may continue to exist in metaplastic or dysplastic mucosa even after successful *H. pylori* eradication, which increases the risk for carcinogenesis and indicates that COX-2 has a crucial role in not only Hp-GC but also nHp-GC (Tsuji et al., 2006). COX-2 overexpression is even thought as a biomarker of intestinal type and earlier stage of GC and an independent prognostic factor for worse survival (Park et al., 2009). COX-2 induces carcinogenesis mainly by inhibiting apoptosis, increasing proliferation and enhancing angiogenesis through multiple pathways including Wnt signalling, p38MAPK / ATF-2 pathway, TLR2 / TLR9 and c-Src-dependent NF-κB activation, MMP-9 and VEGF activation, proteinase-activated receptor-2 signalling, PPARγ inhibition, and so on (Leung et al., 2003; Chang et al., 2004 & 2005; Huang et al., 2006; Li et al., 2009; Zhang et al., 2009;). PGE2, a downstream mediator with central roles in the mentioned COX-2 pathways, plays important functions in both inflammation and carcinogenesis. PGE2 participates in IL-8 production in GECs, facilitates *H. pylori* colonization and persistent infection, and suppresses the immune functions of CD4 (+) T-helper 1 cells by silencing IL-2 gene transcription, which may help accelerate the tumor formation (Takehara et al., 2006; Toller et al., 2010).

During chronic *H. pylori* infection, there are still excessive amounts of reactive oxygen and nitrogen species containing NO and iNOS, which play crucial roles in the stepwise process of GC (Son et al., 2001; Tiwari et al., 2010). NO as an important endogenous carcinogenic factor, correlates with gastric hypoacidity, inhibits p53 expression, increases genetic and epigenetic changes by mediating mutation or DNA methylation, and perturbs the balance between apoptosis and proliferation in GECs (McGee & Mobley, 2000; Lamarque et al., 2003; Shiotani et al., 2004; Chen et al., 2006; Katayama et al., 2009;). Being one of independent prognostic factors, the iNOS overexpression is induced by *H. pylori* infection with involvements of TNF-α, Ras, AP-1, c-Fos and c-Jun, and related to apoptosis, angiogenesis, tumor progression, and poor survival in GC especially of the intestinal type (Tatemichi et al., 1998; Rieder et al., 2003; Chen et al., 2006; Cho et al., 2010). MCP-1 is significantly higher

at mRNA level in poorly differentiated GC, which has effect on COX-2 expression and subsequent PGE2 and VEGF production (Futagami et al., 2008). HGF is more frequently detected in GC tissue than in normal mucosa and shows a concentration-dependent increase under the stimulation of gastrin (Konturek et al., 2001 & 2003). Being the receptor of HGF, c-Met is activated by *H. pylori*, involved in malignant transformation of gastric mucosa and invasive growth of tumor cells, and strongly implicated in late-stage cancer progression and worse prognosis (Zhuang X et al., 2001; Churin et al., 2003; Snider & Cardelli, 2009). In addition, *H. pylori*-mediated GEC invasion depends on c-Met activation, besides on increased activities of MMP-2 and MMP-9 (Oliveira et al., 2006). The c-Met interacts with CagA and suppresses the phosphatidylinositol 3-kinase/Akt pathway, which then leads to β-catenin activation and NF-κB signalling (Suzuki et al., 2009).

4. Immune responses

Another critical aspect of interactions between *H. pylori* and the host are immune responses, which consist of special and unspecialized ones. In fact, immune and inflammatory responses overlap each other especially in roles of many cytokines mentioned above during the infection and carcinogenesis. Herein we mainly focus on important alterations in antibody responses, status of immune cells, balance of cytokines, autoimmune reactions and immune tolerance.

4.1 Antibody responses

A significantly higher seroprevalence has been found in *H. pylori*-infected patients with gastritis, duodenal ulcer, or GC (Przyklenk et al., 1990). Some scientists have concluded that higher *H. pylori* seroprevalence is present in GC patients at early stages of tumor development compared those at advanced stages, whereas others have not (Lin et al., 1993; Klaamas et al., 1996; Komoto et al., 1998). Seropositivity of anti-*H. pylori* IgG is highly prevalent with 76% at 0-4 years and 99% by > or = 18 years of age in a rural population of Africa, where the immunological response is Th2-dominant, which may partly explain the lower risk of Hp-GC (Mbulaiteye et al., 2006). The immune serum-treated *H. pylori* cannot be eliminated *in vitro* by primary human macrophages, although serum enhances the bacteria uptake (Keep et al., 2010). Antibodies are not only dispensable for protection, but they impair both the elimination of bacteria and the development of gastritis. This effect appears to be IgA-dependent and is not a function of specific IgM or IgG antibodies (Akhiani 2005).
The major antibodies responsive to *H. pylori* include IgA and IgG. GC patients elicit different anti-*H. pylori* IgG and IgA responses than the patients with atrophic and superficial gastritis (Manojlovic et al., 2008). IgA>IgG ratio and lower IgG is significantly more frequent in patients with GC and gastric lymphoma than those with gastritis and duodenal ulcer. Correspondingly, higher IgG and IgA levels are often observed in patients with duodenal ulcer or non-atrophic gastritis (Manojlovic et al., 2004 & 2008). As for subclass of IgG response, the IgG1 is lower in GC and AG patients than in gastritis ones; IgG2 is lower for patients with GC localized in the corpus. The IgG1 response in GC patients is correlated with *H. pylori* CagA status (Vorobjova et al., 2006). CagA-positive *H. pylori* strains also seem to markedly frequently induce an IgA response than CagA-negative strains. The presence of serum IgA antibodies likely indicates more severe late outcome of *H. pylori* infection (Rautelin et al., 2000). Anti-CagA antibodies are always higher in GC and AG compared with non-atrophic gastritis. As reported, Hp-GC patients are of 2-3 folds higher in CagA

seropositivity than age-matched *H. pylori*-positive non-GC controls. In addition, anti-CagA antibodies are significantly more prevalent among individuals with elevated titres of *H. pylori*-related IgA than in those only with IgG, with the exception of a small subgroup who later develop GC (Rautelin et al., 2000).

Heat shock protein (HSP) 60 may be associated with *H. pylori*-related gastritis and gastric carcinogenesis. The positivity rate for anti-HSP60 antibody is markedly higher not only in *H. pylori*-positive patients than in *H. pylori*-negative ones, but also in GC patients, especially of the diffuse type, than in *H. pylori*-positive non-GC patients (Tanaka et al., 2009). The isocitrate dehydrogenase (ICD) of *H. pylori*, as an antigen interacting with the host immune system subsequent to a possible autolytic release, significantly elicits humoral immune response and reveals high serum antibody titers in patients with gastritis and ulcer (Hussain et al., 2008). In addition, the *H. pylori*-induced inflammation leads to aberrant glycosylation and demasking of core peptide epitope of mucin 1 (MUC1), which could enhance the host immune responses (Klaamas et al., 2007). IgG immune response to tumor-associated MUC1 is up-regulated among *H. pylori*-infected individuals and related with a higher degree of inflammation in gastric mucosa. The level of anti-MUC1 IgG is positively correlated with that of anti-*H. pylori* IgG in both blood donors and patients with benign diseases, whereas the anti-MUC1 IgM level is not (Klaamas et al., 2007). Moreover, the anti-MUC1 IgG level is notablely higher in GC patients than in blood donors, irrespective of *H. pylori* status or cancer stage. In some individuals, the *H. pylori* infection may stimulate specific response to tumor-associated MUC1 peptide thus modulating tumor immunity (Klaamas et al., 2007).

4.2 Status of immune cells

The infiltration of T, B and macrophage cells always increases at the gastric site of infection with *H. pylori*. The status of T cells and macrophage are closely associated with local and system protective immune responses including native and acquired ones, whereas B cells mainly play more roles in antibody responses and deregulated and exhaustive *H. pylori*-induced T cell-dependent B-cell activation even supports the onset of stomach B-cell lymphoma (D'Elios et al., 2005).

The tumor-infiltrating lymphocytes (TIL) from primary tumors have been isolated and analyzed to characterize the anti-tumor immune responses in GC patients (van den Engel et al., 2006). The CD3 (+) T cell population contains 50% CD4 (+) and 39% CD8 (+) cells. The number of CD19 (+) B cells significantly increases but that of CD3 (+) T cells significantly decreases in intestinal compared to diffuse type of GC. Most of T cell cultures derived from isolated TILs in Hp-GC patients secrete both IFN-γ and IL-5 when stimulated with autologous tumor cells (van den Engel et al., 2006).

There is a significant tendency of Th1/Th2 polarization in patients with *H. pylori* infection, especially of those with CagA positive strains (Wang et al., 2007). Protection against *H. pylori* infection including inhibition of *bacterial* colonization, is mainly mediated by CD4 (+) Th1 cell -mediated immunity (Inoue et al., 2009). Th1-mediated cellular immunity is associated with earlier stages of GC, while Th2-mediated humoral immunity dominates the advanced stages and is negatively associated with an abundance of regulatory T-cells (Treg) (Wang et al., 2007).

Treg cells of positive CD4, CD25 and Foxp3, suppress the host immune response to *H. pylori* infection and have been identified as the major regulatory factor of adaptive immune responses (Kandulski et al., 2010). Vaccine-induced protection against *H. pylori* correlates

with an augmented local recall response in the gastric mucosa, reduced amount of Treg, and increased proportions of neutrophils and CD4 (+) T cells (Becher et al., 2010). The CD4 (+) T cells isolated from stomachs of vaccinated mice can proliferate *in vitro* in response to *H. pylori* antigen, and secrete Th1 cytokines, particularly IFN-γ. The efficiency of these vaccines relates to the alteration of gastric immune responses, from a homogeneous Th1 response to a mixed Th1 and Th2 response (Ernst et al., 2001). The functions of Treg cells are either mediated by direct cell-cell contact or by secretions of the immune-modulating TGF-β1 and IL-10 cytokines (Kandulski et al., 2010). Treg is involved in bacterial persistence, increased in *H. pylori*-associated gastritis, and even positively related with the grade of chronic inflammation and the number of lymphoid follicles (Jang 2010). Treg is also markedly elevated in patients with GC compared to those with chronic gastritis and gastric dysplasia. Additionally, *H. pylori* may direct immunosuppression of T cells and regulate the host immune responses through activation of Treg and dendritic cells (Blanchard et al., 2004).

Macrophages are essential components of innate immunity, and their apoptosis will impair the host mucosal defense to microbes (Asim et al., 2010). *H. pylori* infection leads to a rapid infiltration of macrophages into the mouse stomach. *H. pylori* also activates TLR-2 and TLR-4 in macrophages, and subsequently induces the secretion of distinct cytokines including IL-2, IL-6 and IFN-α (Obonyo et al., 2007). However, the bacteria remain viable when internalized by GECs or even macrophages, which indicates the killing defects in the host due to inhibition of the phagosome maturation (Keep et al., 2010). In addition, *H. pylori* induces the formation of a specific phospho-c-Fos c-Jun activator protein-1 (AP-1) complex in gastric macrophages by an ERK-dependent way, that causes apoptosis and contributes to immune escape of the germ (Asim et al., 2010).

Several *H. pylori* proteins can impair macrophage and T cell functions *in vitro* through unclear mechanisms (Zabaleta et al., 2004). VacA, known as a toxic protein with vacuolating activity, can induce apoptosis in GECs, affect antigen presentation by B lymphocytes, inhibit T cell activation and proliferation, and modulate the T cell-mediated cytokine responses, which mainly target the adapted immune system (Gebert et al., 2004). CagA is also capable of preventing hydroxyurea-induced B-cell apoptosis by reducing p53 accumulation (Umehara et al., 2003). The arginase may impair T cell functions through inhibiting proliferation and the TCR zeta-chain (CD3zeta) expression, besides its role in urea production (Zabaleta et al., 2004).

4.3 Network of cytokines

H. pylori-stimulated host inflammatory and immune responses lead to release of a large amount of cytokines, which contribute to the loss of balance between cell proliferation and apoptosis prior to many gastric lesions including AG and GC. There is a shift from Th1 (IFN-γ, TNF-α and IL-12) towards Th2 (IL-4, IL-10 and IL-6)-type immune response in patients with GC and dysplasia (Marotti et al., 2008). IL-13 is recently described as a central mediator of Th2-dominant immune response and may be implicated in different outcomes of *H. pylori* infection (Marotti et al., 2008). TGF-β and IL-10 are two vital anti-inflammatory cytokines that regulate mucosal immunity in various infectious diseases (Wu et al., 2007). The local and systemic T-cell response in Hp-GC patients is mainly characterized by production of IL-10 (Lundin et al., 2007). When stimulated with *H. pylori* antigens, T cells from both peripheral blood and gastric mucosa produce significantly higher amounts of IL-10 in Hp-GC patients than in *H. pylori*-infected asymptomatic subjects. In addition, the

frequency of activated CD8 (+) T cells is markedly reduced in stomach mucosa of GC patients compared to asymptomatic individuals (Lundin et al., 2007). Therefore, the increased production of the suppressive cytokine IL-10 in Hp-GC patients may lead to a diminished local cytotoxic anti-tumor T-cell response and even contributes to cancer progression.

A predominant *H. pylori*-specific Th1 response associates with peptic ulcer, whereas combined secretion of both Th1 and Th2 cytokines are present in simple gastritis (D'Elios et al., 2005). In *H. pylori*-infected mice, the local Th1-type response might alter the systemic Th1/Th2-type cytokine balance under particular physiopathological conditions of active tissue and/or vascular formation, such as pregnancy (Rossi et al., 2004). *H. pylori* neutrophil-activating protein is able to recruit leukocytes and stimulate neutrophils or monocytes to release IL-12, a key cytokine for the differentiation of naive Th cells into the Th1 phenotype (D'Elios et al., 2007). During *H. pylori* infection, activated macrophages produce IL-18, which stimulates the IFN-γ secretion by NK and T cells (Kawabata et al., 2001). Nevertheless, Th1 immune response in the stomach may destroy the proliferation / apoptosis balance and promote the severity of *H. pylori*-induced gastric lesions (Xia et al., 2001; Vivas et al., 2008).

In the host, the innate immune response usually represents by TLRs and Nod-like receptors that recognize their specific ligands, activate transcription factors including NF-kB, AP-1 and CREB-1, and induce inflammatory cytokines such as IL-8, IL-12, IL-6, IL-1β, IL-18, TNF-α and IL-10 (Sánchez-Zauco et al., 2010). Amounts of the tumor suppressor p53 and the major innate immune hub protein TRAF-6 reduce in *H. pylori*-infected gastric cells, and coincide with a partially cagPAI-dependent decrease in the expression and activity of deubiqutinating enzyme USP7, which indicates that *H. pylori* may also influence some immunity-associated cytokines through interfering in the host ubiquitin pathways (Coombs et al., 2010).

During *H. pylori* infection, significant overexpression of MHC II antigen-presenting genes, IL-7R ubiquitin-D, CXCR4, lactoferrin immune response-related genes, CXCL-2 and -13, CCL18 chemokine ligand, and VCAM-1 genes have been established (Galamb et al., 2008). In addition, IL-23p19 up-regulation is confirmed in gastric biopsies from both *H. pylori* infected-mice and patients with chronic gastritis (Vivas et al., 2008). CCR6 is markedly upregulated in CD3 (+) T cells infiltrating the gastric mucosa and has been reported to mediate lymphocyte homeostasis and immune responses in mucosal tissue (Wu et al., 2007; Tsai & Hsu, 2010). CCL20, the ligand to CCR6, selectively expresses in inflamed stomach tissues and is upregulated in response to *H. pylori* in GECs stimulated by IL-1β and TNF-α. Furthermore, recombinant CCL20 induces lymphocyte chemotaxis migration in fresh gastric T cells *in vitro* (Wu et al., 2007). The interaction between CCR6 and CCL20 plays a potential role in recruiting T cells to inflamed gastric epithelium during *H. pylori* infection (Tsai & Hsu, 2010).

4.4 Autoimmune and immune tolerance

H. pylori has evolved means to structurally alter its surface characteristics to evade innate and adaptive immune responses (Nilsson et al., 2006). *H. pylori* expresses mimicry of some ABO blood group antigens (Moran et al., 2010). Additionally, CagA, VacA and BabA can mimic and bind to specific receptors or surface molecules on GECs and platelets (Höcker & Hohenberġer 2003; Takahashi et al., 2004; Hennig et al., 2004; Baldari et al., 2005). It has been shown that anti-CagA, anti-VacA and anti-BabA antibodies targeting both *H. pylori* components and host mimic molecules can be detected in the majority of GC patients with

increased levels (Rudi et al., 1997; Vaucher et al., 2000; Sokic-Milutinovic et al., 2004). *H. pylori* LPS is of underacylation and underphosphorylation and has significantly lower endotoxic and immuno-activities, which may lead to the infection chronicity (Moran et al., 2010). *H. pylori* produces LPS O-antigen units that can be posttranslationally fucosylated to generate Lewis antigens, which are also found on human GECs, and this molecular mimicry induces autoreactive antibodies (Nilsson et al., 2006). Circulating anti-Lewis antibody is detected in the sera of GC patients but not in *H. pylori*-negative control subjects (Hynes et al., 2005). Absorption of the sera with outer membrane vesicles decreases anti-Lewis autoantibody level. The ability of these vesicles to absorb anti-Lewis autoantibody indicates that they partly play a role in putative autoimmune aspects of *H. pylori* pathogenesis (Hynes et al., 2005).

As reported, C57BL/6 mice infected with CagA (+) *H. pylori* during the neonatal period tend to be protected from preneoplastic lesions, compared to those infected with the same strain at 5-6 weeks of age (Arnold et al., 2011). This protection results from the development of *H. pylori*-specific peripheral immunologic tolerance, which is mediated by long-lived inducible Treg and controls the local CD4 (+) T-cell responses that trigger premalignant transformation. Moreover, both the biased ratio of Treg to T-effector cells in the neonatal period and prolonged low-dose exposure to antigens contribute to the development of immune tolerance to *H. pylori* (Arnold et al., 2011). In addition, exposure of cells to most microbial pathogens can up-regulate HSPs, whereas *H. pylori* decreases expression of HSPs including HSP8, HSP70, HSP60, and heat shock factor 1 (HSF-1). The down-regulation of HSPs may be a mechanism of immune evasion that promotes chronic *H. pylori* infection (Axsen et al., 2009). NO / iNOS as one part of the host innate defense system, determines the killing efficiency of *H. pylori* by macrophages. *H. pylori* up-regulates arginase II (Arg2) expression, resulting in reduction of NO / iNOS production and decreased killing of the germ by macrophages, which implicates another potential mechanism of the immune evasion of *H. pylori* (Lewis et al., 2010).

5. Genetic and phenotypic alterations

Some polymorphisms of certain genes including IL-1, IL-4, IL-6, IL-8, IL-10, TNF, iNOS and COX-2, which likely differ in various host species, play important roles in the inflammation, immune responses, and gastric carcinogenesis, besides in susceptibility to *H. pylori* infection. The GC risk-associated alleles are more prevalent in certain subjects of special human races, geographic regions, and *H. pylori* infection status. Thus, genetic and phenotypic backgrounds of *H. pylori* may interact with mentioned host factors and influence the related biological or pathological processes.

5.1 IL-1

IL-1β and IL-1RN polymorphisms relate to the development of GC and *H. pylori* infection markedly increases the risk, which supports the association of these polymorphisms with risk of Hp-GC (Al-Moundhri et al., 2006). Either infection with vacA s1 (+), vacA m1 (+) and cagA (+) strains or the host genotype of IL-1β -511T homozygous for IL-1RN2/2 allele is associated with an increased GC risk (Figueiredo et al., 2002). Individuals with polymorphisms in IL-1 and TNF-α genes have the highest risk of GC, when they are simultaneously infected by virulent *H. pylori* strains of cagA (+), vacA s1 (+), vacA m1 (+) and babA2 (+). As for IL-1 gene, the odds of developing GC are greatest in those with

combination of high-risk bacterial / host genotypes such as vacA s1 / IL-1β -511T, vacA m1 / IL-1β -511T, cagA (+) / IL-1β -511T, vacA s1 / IL-1RN2/2, vacA m1 / IL-1RN2/2, and cagA (+) / IL-1RN2/2 (Figueiredo et al., 2002).

IL-1β -511T/-31C (+) and IL-1RN2 (+) polymorphisms are associated with severe degrees of inflammation, prevalence of IM and AG, and increased expression of IL-1β, which plays a central role in GC development (Rad et al., 2004). The combined prevalence of *H. pylori* infection and IL-1β -511T genotype has a strong association with GC risk in both Latino and Chinese populations (Morgan et al., 2006; Feng et al., 2008). The IL-1β -511T/T carrier status enhances hypermethylation of multiple CpG island loci and increases the risk for Hp-GC of non-cardiac type as an independent risk factor in a Chinese population (Li et al., 2007; Yoo et al., 2010). IL-1β -511C allele is related with increased risk of AG and GC in Peru (Gehmert et al., 2009). IL-1β -511C/C polymorphism enhances IL-1β production in the antrum, and involves in the development of nHp-GC in North Indian (Kumar et al., 2009). In a Korean population, combined effects of *H. pylori* infection and IL-1β -511C/-31T polymorphisms with enhanced mucosal IL-1β production contribute to the development of intestinal-type GC (Chang et al., 2005). IL-1β -511CC/-31TT variants also increase GC risk in a Chinese population, especially of those with *H. pylori* infection (Yang et al., 2004). Nevertheless, IL-1β -511/-31 alleles are not associated with GC risk in Japan and IL-1β -511T-to-C genotype is not associated with GC in a multistep carcinogenesis model (Kato et al., 2001; Sugimoto et al., 2007). In addition, none of the variants of IL-1β -511C>T, -31T>C, -1464G>C and -3737C>T, is individually or in its haplotype configuration linked to GC in a Caucasian population (Wex et al., 2010).

IL-1β -31C/+3954T haplotypes are more likely detected with IM or dysplasia of the stomach and relate to GC risk in African Americans, but not in Caucasians, Swedes and Italians (Palli et al., 2005; Camargo et al., 2006; Persson et al., 2009; Zabaleta et al., 2011). In Mexico, IL-1β -31C allele increases high-grade dysplasia and is an independent risk factor for GC (Garza-González et al., 2003). The IL-1β -31CC carriers have an increased risk of intestinal-type GC among CagA-positive subjects, compared to those with IL-1β -31TT. Among CagA-negative subjects, however, there is no mentioned association (Sicinschi et al., 2006). IL-1β 1473C>G is significantly associated with GC among Koreans (Lee et al., 2004). In Japan, IL-1β +3953 polymorphism can influence the cancer risk of gastric corpus (Sakuma et al., 2005). Carriers of IL-1β +3954T or IL-1RN2 heterozygote allele cause increased GC risk in a Costa Rican population, although IL-1β -31, IL-1β -511 and IL-10 polymorphisms do not (Alpízar-Alpízar et al., 2005).

IL-1RN1/2 genotype is significantly and independently associated with GC (Erzin et al., 2008). IL-1RN2 allele relates to GC especially in *H. pylori*-positive patients of an Omani Arab population (Al-Moundhri et al., 2006). In Italy, multivariate analyses have shown a notable increase in GC risk for the IL-1RN2 / IL-1β -31T haplotype carriers (Palli et al., 2005). *H. pylori*-infected individuals with carriers of IL-1RN2 show high risks for both intestinal and diffuse types of GC in Asia (Chen et al., 2004). IL-1RN2 and IL-1β -511T may contribute to intestinal GC in the absence of concomitant *H. pylori* infection (Ruzzo et al., 2005). IL-1RN2/2 and IL-1β -31C genotypes relate to higher GC risk in Caucasians (Garza-González et al., 2003). The IL-1RN2/2 genotype is strongly associated with early-stage GC, and involves in the development of nHp-GC in North Indian (Glas et al., 2004; Kumar et al., 2009). IL-1RN 2R/2R and Ex5-35C genotypes are related to an increased risk of Hp-GC of non-cardia type (Crusius et al., 2008). However, IL-1β -511, IL-1RN and IL-2 polymorphisms do not significantly contribute to GC in Korean patients (Shin et al., 2008). In Mexico, IL-1RN2/2 is also not associated with either high-grade dysplasia or risk of GC (Garza-González et al., 2003).

5.2 IL-10

As for subtypes of GC in Taiwanese Chinese, the high IL-10 producer genotype is significantly linked with the risk of cardia type or advanced stage (Wu et al., 2003). The ATA/GCC haplotype of IL-10 -1082/-819/-592 significantly increases GC risk compared with ATA/ATA haplotype (Sugimoto et al., 2007). The -1082G/-819C/-592C alleles (GCC haplotype) usually lead to higher mucosal IL-10 mRNA level than ATA haplotype and are associated with colonization by more virulent *H. pylori* strains of cagA (+), vacA s1 (+), and babA2 (+) (Rad et al., 2004). IL-10 -1082 AG+GG but not -819 or -592 polymorphisms, markedly increase GC risk in China, especially in patients with *H. pylori* infection (Xiao et al., 2009). In a low prevalence province of China, the -1082G* allele is related with significantly increased risk of Hp-GC, whereas the higher susceptibility to GC in -1082 AG+GG genotype does not show a synergism with *H. pylori* status in another population of northern China (Bai et al., 2008). In Korean, the frequency of -1082G carriers is higher in diffuse-type GC or benign gastric ulcer (BGU), regardless of *H. pylori* infection (Kang et al., 2009). Moreover, IL-10 -819CC and IL-1RN 9589TT genotypes are of inverse association with *H. pylori* seropositivity among cases with chronic AG, an established precursor of GC (Gao et al., 2009). The IL-10 819C allele is related with IM in *H. pylori*-positive subjects of a Singapore-Chinese population (Zhu et al., 2009).

In *H. pylori*-infected Japanese, the frequency of -592AA homozygote showing concomitant carriage of HLA DRB1*0405-DQB1*0401 is notably higher in intestinal-type GC. In addition, the HLA class II and -592A/C polymorphism synergistically affect the susceptibility to GC (Ando et al., 2009). IL-10 -592C/A, IL-1β +3954T/C and IL-1RN*2/L are individually associated with GC in Costa Rican regions, and a combination of these cytokine polymorphisms with *H. pylori* vacA s1b / m1 genotypes further increased the risk (Con et al., 2009). IL-10 -592/-1082 alleles are not linked with high-grade dysplasia or GC risk in a Mexican population, though relate to high GC risk in Caucasians; whereas carriers with two or more risk-associated alleles of IL-10 -592C, IL-1β -31C and IL-1RN2 are at increased risk for intestinal-type GC in Mexico, compared to those with 0 or 1 mentioned allele (Garza-González et al., 2003). In Korean, the presence of IL10 -592C/A as opposed to A/A is one of risk factors for IM. The -592CC is associated with more than doubling of the risk for intestinal-type GC. Furthermore, a synergistic effect has been observed between IL-10 -592A/A and IL-8 -251A/A with respect to the development of GC or BGU (Kang et al., 2009). IL-10 -819C and -592C alleles are associated with increased GC risk in Japan, but -1082 polymorphism not (Sugimoto et al., 2007). The -819TT genotype relates to IM and non-cardia GC in an Italian population (Zambon et al., 2005).

Data from Korea have even suggested that the association between IL-10 genetic polymorphisms and GC risk is modified by soybean product intake (Ko et al., 2009). The combined effect between low intake of soybean products and -1082AG/GG, -819TC/CC or -592GG/GA variants will increase the risk for GC. As for subgroups, the CCG haplotype has an increased risk of GC relative to ATA haplotype among subjects with low intake of soybean products (Ko et al., 2009).

5.3 IL-4, IL-6 and IL-8

There is a moderately increased risk for Hp-GC of non-cardia type in IL-4R -29429T variant (Crusius JB et al., 2008). In Taiwanese Chinese, a higher risk of developing cardia or diffuse-type GC is observed for the carrier of IL-4 -590CT/CC genotype (Wu et al., 2003). IL-4 -168C and -590T alleles and IL-6 -174G/G haplotype significantly relate to the risk of non-cardia

GC (Sugimoto et al., 2010). The IL-6 -174G allele is markedly higher in patients with GC than those with chronic gastritis (Gatti et al., 2007).
IL-8 -251A allele significantly increases the risk of gastric dysplasia in Venezuelan subjects, especially of those infected with CagA (+) *H. pylori*, which suggests a role of interactions between host and bacterial genetic factors in the development of precancerous lesions (Kato et al., 2006). Similarly in a Mexican population, the -251A genotype has a significant effect on the prevalence of dysplasia and may be related to distal GC, especially when *H. pylori* CagA is present (Garza-Gonzalez et al., 2007). IL-8 -251A/T allele and polymorphisms in vacA gene are involved in limiting the infection outcome to gastritis and peptic ulcer or in favoring cancer onset in Iranian patients (Kamali-Sarvestani et al., 2006). The -251T>A polymorphism is usually associated with higher IL-8 expression, severe neutrophil infiltration and increased risk of AG and GC in Japan, but not with GC risk in a Portuguese population (Taguchi et al., 2005; Canedo et al., 2008). The IL-8 -251A polymorphism may be associated with progression of AG in *H. pylori*-infected patients, and increase the risks for GC and gastric ulcer in Japanese people (Ohyauchi et al., 2005). The -251A/A genotype, which is more common in *H. pylori*-positive patients with GC or BGU than in *H. pylori*-positive controls, increases the risk for upper-third location, diffuse, poorly differentiated, lymph node and liver metastasis, and p53-mutated subtypes of GC (Taguchi et al., 2005; Kang et al., 2009). The high-risk IL-8 -251T allele is related with >2-fold increased risk for GC of diffused and mixed types (Lee et al., 2005). In addition, the -251T/T genotype significantly relates to increased risk of GC with high frequency of microsatellite instability (Shirai et al., 2006).

5.4 TNF

Polymorphisms of TNF-α -857TT and -1031TT, besides CD14, CXC chemokine receptor 2 (CXCR2), IL-1 RI, NF-κB2, and TLR-4, have the potential to influence persistent *H. pylori* infection (Hamajima et al., 2003). TNF-α -857T/-863A/-1031C alleles are associated with increased risks for gastric ulcer and GC in Japan (Sugimoto et al., 2007). In a Korean population, the -857C/T variant is independently and significantly related to an increased risk of GC regardless of smoking status. However, all haplotype-pairs including TCT or CCC of -863C/A and -1031T/C are linked with a higher GC risk only among smokers (Yang et al., 2009). TNF-α -308 genotypes correlate to higher risk of GC in Caucasians, but not to high-grade dysplasia or increased risk of GC in Mexican population (Garza-González et al., 2003). The -308A allele increases the risk for GC development but is only weakly associated with the early-stage diffuse-type GC (Glas et al., 2004). The -308G/A haplotype relates to an increased IL-8 expression and the susceptibility to GC in several studies. In Poland, GC risk is dramatically relevant to the TNF-α -308G>A and IFN-γ R2 Ex7-128C>T polymorphisms, but not to IL-1α -889C>T and IL-12α IVS2-798T>A, IVS2-701C>A and Ex7+277G>A variants (Hou et al., 2007). Risk of GC is also markedly elevated in Chinese subjects carrying the TNF-α -308 AG genotype (Lu et al., 2005). In addition, polymorphisms in TNF-β (*A and +252G/G) and HSP70-1 (*C and +190C/G) show a significant gene-dose effect as risk markers from preneoplastic lesions to GC in Mexican (Partida-Rodríguez et al., 2010).

5.5 Other cytokine genes

NOS2 -954G/C (especially -954GC+CC) polymorphism but not Ser608Leu is associated with higher risk of GC in a Brazilian population (Jorge et al., 2010). The iNOS C150T is related with the risk of Hp-GC, but not with gastric atrophy or *H. pylori* seropositivity in a Japanese population. Considering the location of GC, there are significant differences between the

controls and non-cardia group for iNOS -150C/T and C/T + T/T (Goto et al., 2006). The iNOS promoter polymorphism of long CCTTT repeat notably upregulates its mRNA level and leads to increased risk of intestinal-type GC in Japanese women, especially of those with IL-1β -31 polymorphism and without smoking history (Tatemichi et al., 2005).
In the high incidence Hexi area of Gansu Province in China, COX-2 -899G>C polymorphism may be a risk factor for GC, and the -899C carrier genotype and *H. pylori* infection possibly have a synergistic effect on GC. However, COX-2 587G>A is not related with GC risk (Zhu et al., 2011). COX-2 -1195AA polymorphism also plays an important role in developing GC in another high-risk Chinese population (Zhang et al., 2006). COX-2 -765G>C polymorphism might be a marker for genetic susceptibility to GC in northern India, regardless of *H. pylori* infection (Saxena et al., 2008). Moreover, the lymphotoxin-α NcoI A/G heterozygous genotype correlates to *H. pylori* infection in noncardia GC patients of Chinese Han population (Li et al., 2005). And in Cauca population, the glutathione S-transferase M1 homozygous deletion polymorphism is related to increased GC risk (Torres et al., 2004).

6. Beneficial edge of the sword

In recent years, increasing data have indicated that patients with Hp-GC prospectively have a better outlook than those with nHp-GC (Meimarakis et al., 2006; Marrelli et al., 2009). *H. pylori* infection must play certain roles as the other edge of the sword, which is beneficial for the host and counteracts its harmfulness in pathological lesions including gastritis, GC, and lymphoma. However, up to date, the corresponding studies and results are still limited because of multiple influencing factors including traditional unilateral opinions.
The positive interaction between *H. pylori* and the host should be the radical factor in leading to changes of local and system immune responses. There is a high *H. pylori* prevalence but a low GC risk in *H. pylori*-infected than in uninfected Mexican children, which may be attributed to significantly higher infiltration of macrophages and T and B cells, a balanced increase of CD4, CD8, and CD20 lymphocytes, but decreased levels of activated mast cells, neutrophil and mononuclear cells (Muñoz et al., 2007). During *H. pylori* infection, both the number of local CD4 (+) T cells and MHC II expression by the GECs increase, and GECs can process and present antigens to CD4 (+) T cells as a new kind of local antigen presenting cells (APC) (Barrera et al., 2002). Therefore, *H. pylori* infection in the host may alter natural immune mechanisms against cancer.
The humeral immune response induced by *H. pylori* is predominately IgG1 subclass (suggestive of a Th2 response) and likely protects against the development of GC, although it is not essential for bacterial eradication (Segal et al., 2001). As reported, the antibody level of anti- Thomsen-Friedenreich antigen (TAg) in GC patients is significantly lower than that in normal blood donors (Klaamas et al., 2002). However, TAg-specific IgG immune response is up-regulated exclusively in *H. pylori*-infected individuals, which may contribute to the significantly better survival of Hp-GC patients at early stage than that of nHp-GC ones at the same stage. Better survival is also noted in *H. pylori* seropositive IgM strong responders at approximately 40-60 months of observation, though the anti-T IgM level is not significantly related to the survival (Kurtenkov et al., 2003). In addition, the stimulation of *H. pylori*-related autoantibodies in antigen processing and presentation and subsequent T-cell activation and proliferation improves host immune status. On the other hand, in an autoimmune response, autoantibodies can induce the cross-reaction against those localized

or circulating GC cells, which are characterized by mimic or absorbed *H. pylori* antigens, and lead to the killing and even suppressing of metastasis of cancer cells (Xue et al., 2008). Thus, it is hypothesized that autoimmune responses induced by *H. pylori* components may help improve the prognosis of GC patients.

Several models, including delayed type hypersensitivity in immune mice, and spontaneous clearance of *H. pylori* from IL-10 and phagocyte oxidase mice, provide evidence that severe inflammation may be sufficient to eradicate the germ (Blanchard et al., 2004). *H. pylori* LPS can dramatically initiate inflammatory responses and cause severe pathological changes not only *in vitro* but also *in vivo*. However, increased levels of TNF-α and IL-10, as well as a strong antigen specific Th1 response including, IFN-γ, IL-2 and high IgG2a serum titers are simultaneously observed in mice inoculated with *H. pylori* LPS+ sonicate. Mice that received LPS- sonicate are strongly Th2 biased in their immune response, with significantly more IL-4 than IFN-γ and serum IgG1 titers higher than IgG2a (Taylor et al., 2006). Accordingly, *H. pylori*-induced inflammatory responses potentially have positive functions in resisting certain cancer-advancement-related biological processes post the development of GC and showing better outlook in those patients, although they have played fundamental roles during the phase of cancer formation.

Interestingly, the COX-2 expression induced by *H. pylori* still seems to be able to attenuate the degree of AG, the initial event of GC, though it plays a role in gastric carcinogenesis (Hahm et al., 2002). COX-2-dependent PGE2 also shows a protective effect during the oncogenic process of Hp-GC in that it can prevent *H. pylori*-induced gastric preneoplasia and reverse preexisting lesions by suppressing IFN-γ expression (Toller et al., 2010). As confirmed, the protective effect is always accompanied by increased bacterial colonization in models, which is attributed to the IL-2-dependent immunosuppressive effects of PGE2 on CD4 (+) Th1 cells in migration, proliferation and cytokine secretion. Therefore, PGE2 has an important immunomodulatory role during *H. pylori* infection, preventing excessive local immune responses and the associated immunopathology by inhibiting the effector functions of pathogenic Th1 cells (Toller et al., 2010).

Certain genetic and phenotypic polymorphisms also show beneficial effects in improving the prognosis of GC patients, which might differ in various populations and need further confirmation. IL-6 -572G carrier is found to have a protective effect against IM development as compared with C/C (Kim et al., 2008). IL-8 -251AA genotype confers a decreased risk for Hp-GC of non-cardia type, mainly of the intestinal type (Crusius et al., 2008). IL-10 -592C/C is an independent factor associated with a decreased risk of intestinal-type GC by multivariate analysis (Kang et al., 2009). When analyzed together with host genetic factors, the presence of the IL-1β -31TT genotype emerges as a protective factor against gastric malignant disorders (Erzin et al., 2008). Based on a review of 25 case-control studies in Caucasian, Asian and African populations, IL-1β and NAT1 variants are most consistently associated with increased GC risk, which may account for up to 48% of attributable risk of GC, but HLA-DQ, TNF and CYP2E polymorphisms may confer certain protection against GC (González et al., 2002). However, a comprehensive analysis of 207 SNPs of 11 Cytokine genes including IL-1α, IL-1β, IL-1RN, IL-4, IL-4R, IL-8, IL-10, IL-12, TNF-α, TNF-β, and IFN-γ, has revealed that just variations in IL-4 (984 and 2983 AA/GA) and IL-1RN (-1102 and 6110 CG/GA) diplotypes are negatively associated with the risk of Hp-GC (Seno et al., 2007).

7. Conclusion

The majority of GC relates to chronic inflammation induced by *H. pylori* infection, in which many bacterial virulence factors including Cag PAI, VacA, OMP, LPS, urease, IceA, and flagella components participate with fundamental roles through a complex network of inflammatory cytokines, multiple signalling pathways, and even some genetic or phenotypic polymorphisms of the host. Gastric carcinogenesis, especially of the intestinal-type tumor, is a multistep process of mucosal alterations leading from gastritis via glandular atrophy, IM and dysplasia to invasive carcinoma (Bornschein et al., 2010). There is a potential 'point of no return' during this process, which means a situation when certain alterations are no longer reversible by *H. pylori* eradication and progression to GC have to continue (Vieth et al., 2006; Bornschein et al., 2010). Thus, the gastric carcinogenesis is actually divided into two phases; one is of reversible pre-the-'point of no return', and the other is of irreversible post-the-'point of no return'. During the first phase, *H. pylori* works with more roles as a confirmed carcinogen according to traditional opinion; whereas in the second phase, the inflammation has been switched to *H. pylori*-independent carcinogenesis with GC as the destination.

Considering the host-bacterium cross-talk background and described double functions of both inflammatory / immune responses and genetic / phenotypic polymorphisms, a novel angle should be adopted to analyze the roles of *H. pylori* as a double-edged sword in GC. *H. pylori* is more harmful in promoting carcinogenesis prior to the 'point of no return', however, may be more beneficial for improving the host outlook post the development of GC. Based on this theory, *H. pylori* eradication may be performed at proper stage to protect against GC, and more efficient vaccines of prophylaxis and therapeutic ones might be designed and used to prevent the advancement of GC and improve the prognosis, which needs further confirmation by large from-bench-to-bed studies.

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9. References

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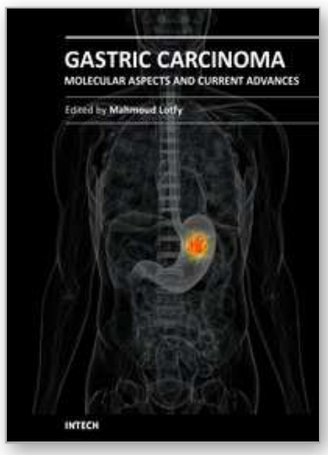

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Gastric cancer is one of the most common tumors worldwide. It has a heterogeneous milieu, where the genetic background, tumor immunology, oxidative stress, and microbial infections are key players in the multiple stages of tumorigenesis. These diverse factors are linked to the prognosis of the gastric cancer and the survival of gastric cancer patients. This book is appropriate for scientists and students in the field of oncology, gastroenterology, molecular biology, immunology, cell biology, biology, biochemistry, and pathology. This authoritative text carefully explains the fundamentals, providing a general overview of the principles followed by more detailed explanations of these recent topics efficiently. The topics presented herein contain the most recent knowledge in gastric cancer concerning the oncogenic signaling, genetic instability, the epigenetic aspect, molecular features and their clinical implications, miRNAs, integrin and E-cadherin, carbohydrate-associated-transferases, free radicals, immune cell responses, mucins, Helicobacter-pylori, neoadjuvant and adjuvant therapy, prophylactic strategy for peritoneal recurrence, and hepatic metastasis.

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Slavka Krautzeka 83/A
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Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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