TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

Cytokines, cytokine gene polymorphisms and *Helicobacter pylori* infection: Friend or foe?

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Core tip: In this review, we present the cytokine profiles of infection and the main cytokine gene polymorphisms associated with resistance/susceptibility to *Helicobacter pylori*. We also discuss how such polymorphisms may influence infection/disease outcomes.

Abstract

Helicobacter pylori (*H. pylori*) is a flagellated, spiral-shaped, microaerophilic Gram-negative bacillus that colonises the gastric mucosa of more than 50% of the human population. Infection is a risk factor for gastritis, ulcer disease and stomach cancer. Immunity against *H. pylori* is mainly related to Th1/Th17 skewing, and the activation of regulatory T cells is the main strategy used to limit inflammatory responses, which can result in the pathogen persistence and can lead to chronic gastrointestinal diseases, including cancer. Furthermore, host genetic factors that affect cytokines may determine differences in the susceptibility to many diseases. In this review, we present the cytokine profiles and the main cytokine gene polymorphisms associated with resistance/susceptibility to *H. pylori* and discuss how such polymorphisms may influence infection/disease outcomes.

HELICOBACTER PYLORI

Helicobacter pylori (*H. pylori*) is a flagellated, spiral-shaped, microaerophilic Gram-negative bacillus that colonises the gastric mucosa, causing gastroduodenal diseases such as chronic gastritis, ulcer disease and gastric cancer[1]. *H. pylori* infection is the major environmental risk factor for non-cardia gastric adenocarcinoma. Although it is estimated that 50% of the population worldwide is infected by this bacterium, only a subset of 1% to 2% of those individuals will develop gastric malignancies[2,3]. The prevalence of *H. pylori* infection may vary depending on the studied population. Furthermore, researchers have associated the increased prevalence of *H. pylori* infection with socioeconomic indicators, as the incidence of infection is higher in developing countries[4].

H. pylori infection is associated with poor hygiene conditions[5]. Although the transmission mechanism of *H. pylori* has not been completely elucidated, evidence suggests that human-to-human spread *via* oral-oral or faecal-oral routes are important mechanisms[6]. The main mechanism of *H. pylori* survival in the stomach is due to the action of urease, which hydrolyses the urea present in the stomach into CO_2 and ammonia, which then neutralise stomach acidity. These components are essential for neutralising gastric acid and promoting a favourable environment for *H. pylori* survival in the stomach[7,8].

H. pylori starts colonisation of the gastric mucosa by crossing the gastric mucus layer and adhering to the gastric epithelium, where it obtains the necessary nutrients and simultaneously avoids attack by the host immune system[1]. The inflammation caused by *H. pylori* infection is generated by multiple pathways from both the gastric epithelial cells, which are the host first line of defence against this organism, and the circulating immune cells recruited to the site of infection[9].

Several mechanisms of *H. pylori* pathogenicity have been described, including modification on host gene expression, decreased gastric acid secretion, infection-induced cell proliferation, epithelial cell elongation, degradation of cell-cell junctions and the production of systemic and mucosal IgA and IgG antibodies. However, the effect of antibody production on bacterial colonisation has not been completely elucidated[10].

The major pathogenicity factors of *H. pylori* include the virulence components vacuolating toxin (VacA), cytotoxin-associated gene A product (CagA) and γ-glutamyltranspeptidase (GGT), in addition to pathogen-associated molecular patterns (PAMPs) including lipopolysaccharide (LPS) and flagella[11]. The CagA+ strains are more potent in causing gastric mucosal damage than the CagA- strains[12]. Several studies have shown the importance of CagA in *H. pylori*-induced inflammation and suggest that CagA plays a role in nuclear factor kappa-B (NF-κB) activation and interleukin-8 (IL-8) production[2]. Moreover, the ectopic expression of CagA induces NF-κB nuclear translocation and IL-8 production in gastric epithelial cells[12].

Another crucial element required for the persistence of *H. pylori* infection is related to the secretion of the VacA protein, which is reported to inhibit both T cell proliferation and the production of the transcription factors necessary for IL-2 production[13]. VacA also induces the production of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), macrophage-inflammatory protein-1α, IL-1β, IL-6, IL-10 and IL-13 in a dose-dependent manner without causing the degranulation of mast cells[14]. Thus, *H. pylori* virulence factors play an important role in the infection and act by down-modulating immunity against the bacterium.

IMMUNITY TO *H. PYLORI*

Colonization of the stomach by *H. pylori* elicits an inflam-

matory response and recruits neutrophils, lymphocytes, macrophages and dendritic cells (DCs) to the gastric mucosa (Figure 1)[15]. The molecular mechanisms by which *H. pylori* triggers and maintains the local immune response are complex, but there is evidence that cytokines produced by both innate and adaptive immune systems can lead to the development of ulcer disease, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma[13].

The initial interaction between *H. pylori* and the innate host immune response is mediated through surface receptors expressed on gastric epithelial cells and antigen-presenting cells (APCs - DCs and macrophages). Integrins may recognise virulence factors excreted by the bacterium, and pattern recognition receptors (PRRs) such as Toll-like receptors (TLR) and Nucleotide-binding oligomerisation domain receptor 1 (NOD1) interact with bacterial PAMPs[14,16].

The activation of human gastric DCs by *H. pylori* directs naïve CD4+ T cells to Th1 differentiation through IL-12 production and enables these cells to secrete cytokines such as IL-1, IL-6, TNF-α and IFN-γ by activation of the transcription factors T-bet (T box expressed in T cells) and Stat 4 (signal transducer and activation of transcription factor 4)[17]. This differentiation is dependent on IL-18, which is a Th1-related cytokine that promotes IFN-γ production by T cells and natural killer (NK) cells in the presence of IL-12 and is correlated with gastric inflammation[18,19]. The initial Th1 response aims to eradicate the *H. pylori* infection. However, in some individuals Th1 cell-producing cytokines sustain the mucosal inflammation and contribute to the development of the infection-associated gastric preneoplastic immunopathology that manifests histologically as atrophic gastritis, epithelial hyperplasia and intestinal metaplasia[17].

Although it is expected that Th2 immune responses are required for protection against extracellular bacteria, Th2 cells are weakly associated with *H. pylori* infection[20]. However, a predominant Th2 immune response is characterised by IL-13 secreting cells. A Th2 response has been observed in patients with *H. pylori*-related intestinal metaplasia and intestinal-type gastric cancer, suggesting that Th2 cells could be involved in different outcomes of *H. pylori* infection[21].

In infected individuals, a Th2 response induces IgG1 production while a Th1 response contributes to significant increase in the overall levels of IgG2 through IL-2 and IFN-γ production. IgG2 titres are higher than IgG1 titres in *H. pylori*-infected patients, particularly those with ulcer disease[22]. Studies have reported that gastric cancer risk is positively correlated with higher serum antibody levels against *H. pylori*[23]. However, it has also been shown that weak serum IgG antibody responses against CagA may be associated with the risk of gastric cancer development, suggesting that CagA might play a role in carcinogenesis[24].

In addition to Th1/Th2 immune responses, Th17 cells also contribute to mucosal host defence by function-
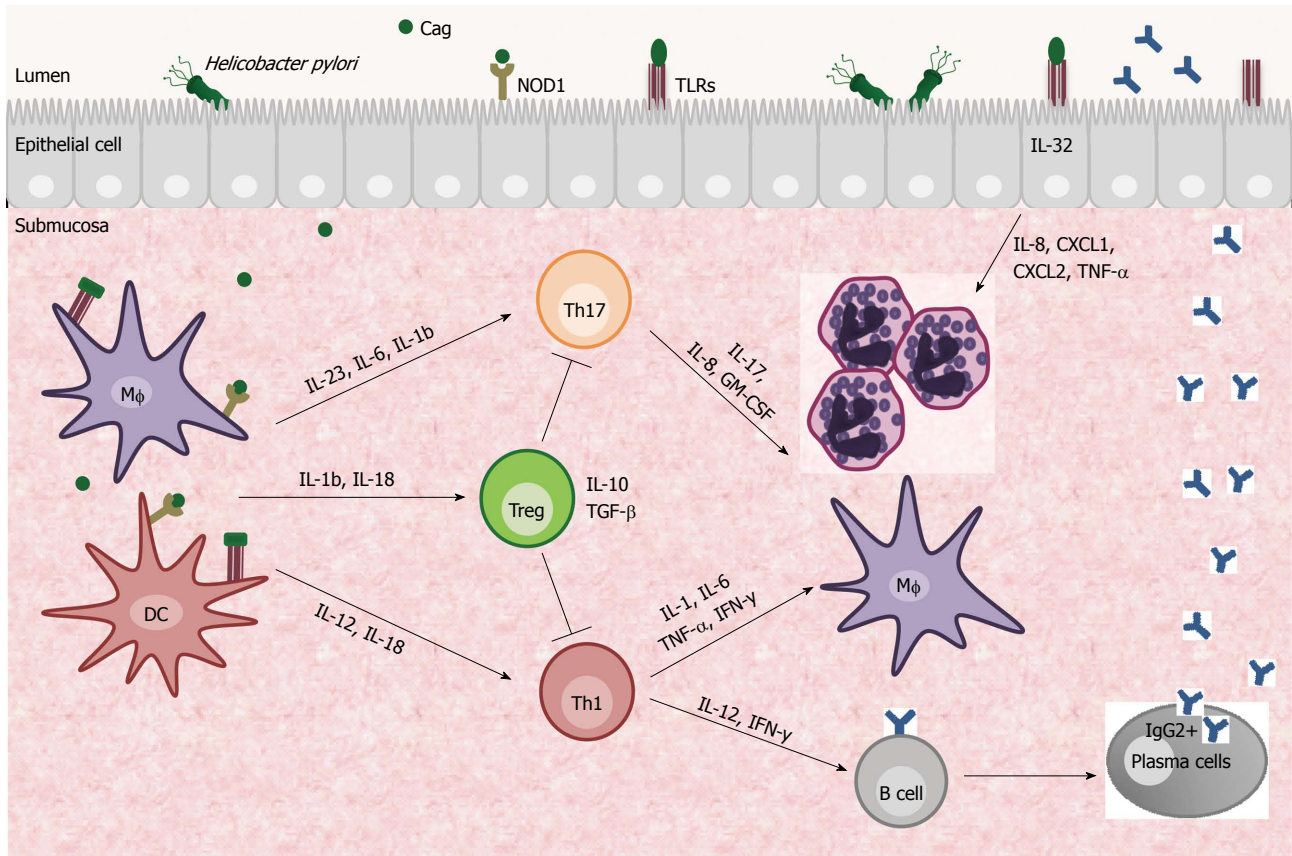
Figure 1 Immunological response elicited by *Helicobacter pylori* infection. The presence of *Helicobacter pylori* (*H. pylori*) cytotoxins (VacA, CagA, CagL and GGT) and PAMPs (flagella, lipopolysaccharide) in the gastric mucosa activate antigen-presenting cells (APCs), such as dendritic cells and macrophages. These cells stimulate the adaptive immune response through the production of cytokines, such as IL-12 and IL-23, which activate Th1 and Th17 cells, respectively. The cytokines induce an inflammatory process characterization by the recruitment of neutrophils, lymphocytes, macrophages and dendritic cells. Th1 cells release IL-2 and IFN-γ and stimulate B cell differentiation and anti-*H. pylori* IgG production from secretory plasm cells. Furthermore, epithelial cells recognize the *H. pylori* antigens and produce IL-32, which induces chemokines and contributes to inflammation. In individuals infected with CagA+ *H. pylori*, Treg cells are activated by APCs through IL-18 and IL-1β to modulate the immune response and contribute to persistent infection. Consequently, *H. pylori*-associated pathologies, such as chronic gastritis and gastric adenocarcinoma, may develop. MF: Macrophages; DC: Dendritic cells; PAMPs: Pathogen-Associated Molecular Patterns.

ing as mediators of the inflammation associated with the production of IL-17, IL-8 and granulocyte macrophage colony-stimulating factor (GM-CSF), which are used to attract granulocytes. An increased IL-17 response depends on IL-6, IL-23 and CCL20 expression by *H. pylori*-stimulated macrophages and is regulated by Stat3 and the NF-κB pathway[25]. *H. pylori*-stimulated DCs are potent inducers of Th17 cells by regulating IL-1β/IL-23 production, and the virulence factor CagA may play an important role in mediating this process[26].

H. pylori-specific Th17 cells persist in the blood and gastric mucosa of individuals after *H. pylori* eradication and can be associated with the persistence of gastric inflammation following *H. pylori* eradication observed in both animal models and humans[27]. Th17 persistence has been shown to be a consequence of IL-1β levels, which remain elevated in the gastric mucosa and might favour the low-level proliferation of Th17 cells previously recruited into the gastric mucosa during active *H. pylori* infection[28].

In contrast to potent pro-inflammatory responses, neither Th1 nor Th17 cells are by themselves absolutely essential for the spontaneous control of *Helicobacter* infections. These data suggest that both Th subsets act synergistically or that there might be other Th subsets involved in the process[29]. Recently, it was shown that the expression of the intracellular pro-inflammatory cytokine IL-32 is induced in gastric epithelial cells by *H. pylori* in a Cag Pathogenicity Island (PAI)-dependent manner. IL-32 activates NF-κB and stimulates the production of cytokines and chemokines, including IL-8, CXCL1, CXCL2, and TNF-α; IL-32 high levels are also related to human gastritis and gastric cancer[30]. Further studies are necessary to clarify the role of IL-32 in *H. pylori*-infected gastric mucosa.

Despite inciting inflammation, the clearance of *H. pylori* is often incomplete due to the activation of CD4+CD25hi forkhead box protein 3 (Foxp3+) regulatory T cells (Tregs). Treg cells are potent suppressors of T cell effector function and regulate the balance between immunity and infection[31]. Treg cells have been implicated in limiting inflammatory responses to *H. pylori* by producing anti-inflammatory cytokines such as IL-10 and TGF-β that, in some circumstances, result in pathogen persistence

to limit tissue injury. This process is positively correlated with chronic gastritis and gastric adenocarcinoma[31,32].

H. pylori infection is known to suppress host immune responses. However, the mechanism of this suppression is poorly understood, although it is hypothesised that the suppression is caused by efficient DC re-programming toward a tolerance-promoting phenotype *via* IL-1β and IL-18. These DC cells have the capacity to induce Treg cell production through mucosal expression of transforming growth factor-beta 1 (TGF-β1) and IL-10[33-35]. This regulation seems to be dependent on the CagA virulence factor, and only CagA+ *H. pylori* promotes IL-10 expression, inhibiting DC maturation and inducing DCs to have a tolerogenic phenotype which can suppress the proliferation of CD4$^+$ and CD8$^+$ effector T cells[36]. The functional outcome is the suppression of *H pylori*-specific Th17 and Th1 immunity and chronic colonization of the stomach[36,37].

Previous reports have demonstrated that the gastric mucosa of *H. pylori*-infected children contained higher numbers of Treg Foxp3$^+$ cells and increased levels of IL-10, TGFβ1 and IL-6 compared to infected adults[38,39]. Thus, reduced gastric inflammation, including diminished neutrophil accumulation, in *H. pylori*-infected children compared to infected adults is likely due to the downregulation of gastric Th17 and Th1 responses caused by enhanced mucosal regulatory T-cell activity in children[39,40]. The down-regulated Th17 responses in the gastric mucosa of *H. pylori*-infected children might account for the susceptibility of children to the infection and to the persistence of infection. Additionally, there may be important implications in the development of an effective anti-*H. pylori* vaccine because IL-17 has been described as a key mediator of vaccine-induced reduction of *H. pylori* infection[39,41].

The enhanced Treg response induced by *H. pylori* chronic infection has been shown to modulate coexisting inflammatory disease by conferring protection against allergies, asthma and inflammatory bowel diseases[42]. An epidemiological study revealed an inverse association of asthma with seropositivity to *H. pylori* that was CagA-dependent. This result demonstrates the importance of the CagA virulence factor in inducing immune regulation[43].

The way certain individuals respond to *H. pylori* infection and how the immune cells are recruited to *H. pylori* may determine their susceptibility/resistance immune profiles to the bacterium. Furthermore, cytokine polymorphisms may play important roles in *H. pylori* pathogenicity.

CYTOKINE POLYMORPHISMS AND *H. PYLORI* INFECTION RISK

The exon sequences of genes encoding cytokines and cytokine receptors are generally conserved. However, mutations in other gene regions that do not affect the amino acid sequence can be found. These polymorphisms may affect protein expression in various ways, including lev-

els of gene transcription, splicing, stability and levels of mRNA translation[44]. Polymorphisms in cytokine genes may influence the development of several diseases[45]. Susceptibility to many diseases is associated with a particular "pro-inflammatory" profile that can be explained by individual genetic determinants. Host genetic factors that affect cytokine polymorphisms may determine why some individuals infected with *H. pylori* develop gastric cancer while others do not[46].

Several studies have evaluated the direct association of *H. pylori* infection with cytokine gene polymorphisms. Figure 2 presents the gene polymorphisms that were previously evaluated in association studies with risk for *H. pylori* infection. These genes include the following: *IL-1R*, *IL-1B*, *IL-1A*, *TNF-α*, *IL-6*, *IL-4*, *IL-13*, *IL-12*, *IL-2* and *IL-10*[47-52]. To generate Figure 2, a systematic literature search was performed using Web of Science and PubMed. We searched for articles published from March 2000 until May 2013 using the following keywords: "*H. pylori* infection", "*H. pylori* and polymorphism", and "*H. pylori* and cytokine polymorphism and association". We excluded the articles that had no full text available. Our results indicate that statistically significant associations were observed for *IL-1R*, *IL-1A*, *IL-2* and *TLR* polymorphisms.

Many studies have examined the potential modulatory effect of *H. pylori* infection on the association between genetic polymorphisms and the risk of gastric cancer, ulcer disease, gastritis and lymphoid follicle lymphoma development[53-60]. Several gene polymorphisms have been reported; the most frequently studied are in the *IL-1*, *IL-10* and *TNF-α* genes.

There are three members of the interleukin IL-1 gene family: *IL-1A*, *IL-1B*, and *IL-1RN*, which encode the pro-inflammatory cytokines IL-1α, IL-1β and the endogenous anti-inflammatory cytokine IL-1ra, respectively. The IL-1 gene cluster is located on chromosome 2q and contains three related genes within a 430-kb region[61]. The *IL-1RN* gene has a penta-allelic 86-bp variable number tandem repeat in intron 2. The *IL-1RN* gene is associated with a wide range of chronic inflammatory diseases and enhanced IL-1β secretion[62].

Tseng *et al*[52] investigated the relationship between the risk of *H. pylori* antibody seropositivity and cytokine gene polymorphisms among Jamaican children. They observed a negative association between *IL-1A* -889 allelic polymorphisms and the presence of *H. pylori* antibodies. Hartland *et al*[48] reported a positive association for *IL-1R* +1622 and *H. pylori* infection. However, no association was observed for *IL-1RN* polymorphisms[48,50] or the *IL-1R* +1498 polymorphism[48] and the risk of *H. pylori* infection.

Two diallelic polymorphisms at positions -511 and -31 in *IL-1B* have been extensively studied in several diseases. El-omar *et al*[46] reported that interleukin-1 gene cluster polymorphisms are associated with an increased risk of both hypochlorhydria induced by *H. pylori* and gastric cancer. Based on their results, several studies have
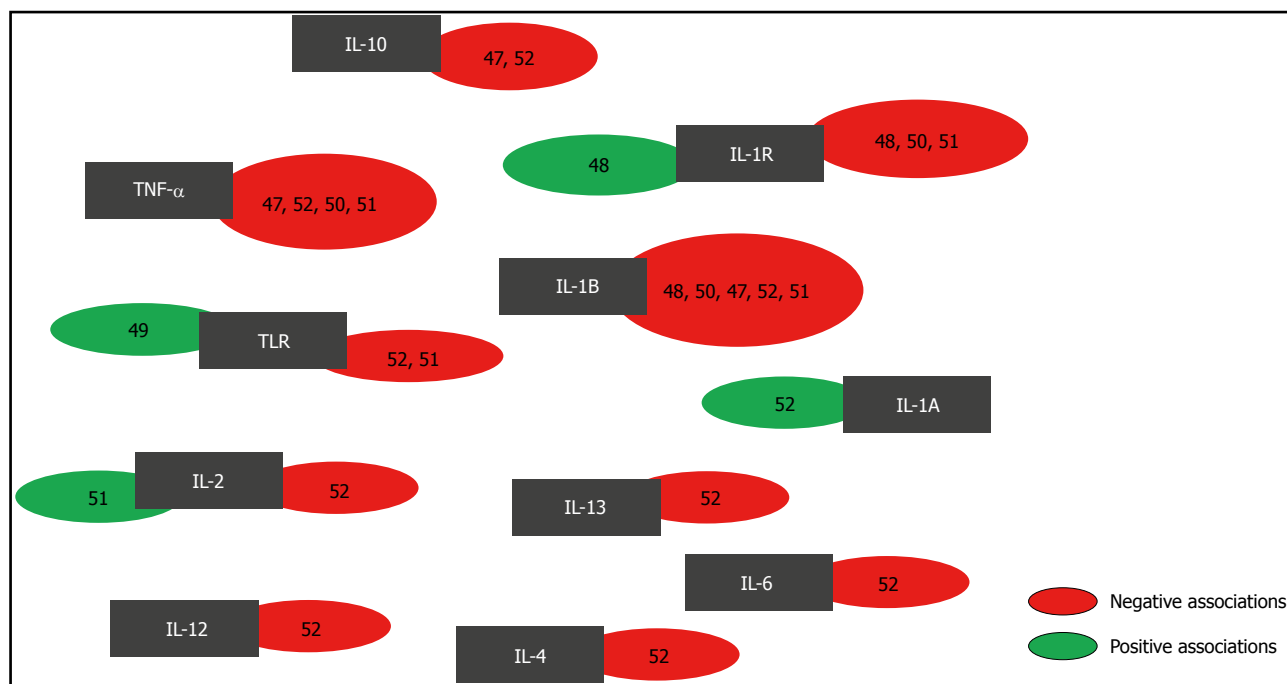
Figure 2 Diagram of the polymorphisms evaluated for risk of *Helicobacter pylori* infection. The black boxes contain the cytokines that were studied. In the green boxes on the left are the references of works that identified associations between polymorphisms and *Helicobacter pylori* (*H. pylori*) infection, and the red boxes on the right contain the references of publications that identified no associations of polymorphisms with *H. pylori* infection.

examined the relationship of *IL-1* polymorphisms with *H. pylori* infection in gastrointestinal diseases[63-66].

Studies have shown that gastric adenocarcinoma and ulcer disease have distinct effects on gastric secretions. Gastric cancer is associated with low gastric acid production, whereas ulcer disease is associated with high levels of gastric acid secretion[67,68]. IL-1β is also a potent inhibitor of gastric acid secretion[69,70]. IL-1β is upregulated in the presence of *H. pylori* and plays an important role in the initiation and amplification the inflammatory responses to infection[71-73].

The *IL-10* gene is located on chromosome 1 (1q31-1q32). Many single-nucleotide polymorphisms (SNPs) have been identified in the IL-10 gene promoter region. Three polymorphic promoter variants in *IL-10* are located at positions -1082, -819 and -592. These SNPs have been frequently studied, and gene variants are associated with increased IL-10 production[74,75].

Our group recently submitted a study that evaluates IL-10 gene polymorphisms and the risk of *H. pylori* infection. We identified associations for 4 SNPs that were risk factors for *H. pylori* infection (data not shown). Furthermore, 8 SNPs were associated with spontaneous IL-10 production, suggesting that *IL-10* polymorphisms can modulate the levels of cytokine production and can thus modify the risk of *H. pylori* infection. Interestingly, statistically significant associations were identified between the *IL-10* polymorphisms at positions -1082[57] and -592[63] and gastric cancer risk only in individuals infected by *H. pylori*. An increased risk of gastric cancer was observed in patients who carry these polymorphisms and are infected by *H. pylori*, suggesting a synergistic effect for the combina-

tion of host genotype and the presence of the bacterium.

The *TNF-α* gene is located within the human major histocompatibility complex (MHC) on chromosome 6p21.3. An important SNP that has been studied is located at position -308 in the promoter region. One mechanism regulating the expression of TNF-α occurs at the transcriptional level. Studies evaluating the relationship between *TNF-α* polymorphisms and *H. pylori* infection have found no associations[47,52]. However, many studies suggest that *TNF-α* polymorphisms are potential determinants of gastric disease susceptibility[76]. In contrast, Chakravorty *et al*[54] observed a negative association between the *TNF-α* -1031 polymorphism and ulcer disease only in patients infected by *H. pylori*.

The SNP *TLR* -113T/A was negatively associated with *H. pylori* seroprevalence[49]. However, no association with *H. pylori* seroprevalence was found with SNP *TLR* +636[52]. Furthermore, there were no significant associations between SNPs on *TLR2* Arg677Trp, *TLR2* Arg-753Gln, *TLR4* Asp299Gly and *TLR5* 392STOP and the risk of *H. pylori* infection[51].

No significant associations were found for SNPs *IL-6* -597 G/A, *IL-6* -572G/C, *IL-6* -174 G/C, *IL-4* -524 T/C and *IL-13* -1069C/T[52]. These results suggest that more studies are needed to elucidate the roles of these polymorphisms as risk factors for *H. pylori* infection.

In the *IL-2* gene, the T330G polymorphism was negatively associated with *H. pylori* infection and was responsible for increasing the serum IL-2 levels in *H. pylori*-positive adults and children[51]. The same polymorphism in the *IL-2* gene was not an important contributor to the pathogenesis of ulcer disease, gastric cancer and ulcer

disease in Korean patients[65]. This result suggests that genetic variations between ethnicities could influence *H. pylori* susceptibility and infection outcomes.

Sequencing of the IL-12 p40 gene revealed a TaqI restriction fragment length polymorphism in the 3'-untranslated region at position 1188 (A>C). Although there are inter-individual variations in IL-12 production levels, this cytokine is not involved in defining the genetic basis for peptic ulcer susceptibility[77,78]. Several studies have evaluated the impact of *IL-12* gene SNPs in *H. pylori*-infected patients. Three SNPs tested in IL-12A (IVS2 -798 A>T, IVS2 -701 A>C and Ex7 +277 A>G) were not related to gastric cancer risk[79], while the other 2 SNPs (*IL-12A* 2504 and *IL-12B* +15485) were correlated with non-cardia gastric adenocarcinoma[80].

These studies support the hypothesis that a combination of host genotype and the presence of *H. pylori* could be crucial for the development of gastric diseases. More studies are necessary to explain the consequences of genetic polymorphisms at the cytokine level and their functions in and impacts on *H. pylori* susceptibility. Additional studies may provide support for new strategies of vaccine production against this infection.

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