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REVIEW ARTICLE

Role of inflammatory gene variants in *Helicobacter pylori*-related gastric cancer*

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Abstract

Helicobacter pylori-related gastric cancer results from a chronic inflammatory process that arises from atrophic gastritis, and develops into intestinal metaplasia, hyperplasia, and eventually gastric adenocarcinoma. Although approximately half of the world's population is infected with *Helicobacter pylori* (*H. pylori)*, less than 3% of these infected individuals develop gastric cancer. *H. pylori* infection can cause both acute and chronic inflammation, and may be present for decades within its host. Inflammatory gene variants are particularly important factors that may influence a host's susceptibility to *H. pylori*-related gastric cancer. The inflammatory gene variants uncovered thus far include interleukin gene clusters, tumor necrosis factor-α, Toll-like receptors (TLRs), and inflammatory gene polymorphisms found in genome-wide association studies (GWAS). The association between these gene variants and the risk of *H. pylori*-related gastric cancer will aid in our understanding of the pathogenesis of gastric cancer in order to prevent and defeat this malignancy.

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Gastric cancer is a disease that affects people worldwide, and is the second leading cause of cancer-related deaths [1]. China is the country with a high incidence of gastric cancer, and in 2002, approximately 41% of new gastric cancer cases worldwide were from China [2]. *Helicobacter pylori (H. pylori)* infection is the primary cause of gastric cancer, and contributes to an estimated 32% risk of developing gastric cancer [3]. *H. pylori*-related gastric cancer results from a chronic inflammatory process that arises from atrophic gastritis, and develops into intestinal metaplasia, hyperplasia, and eventually into gastric adenocarcinoma [4]. The World Health Organization has classified *H. pylori* as a class I human carcinogen [5]. Approximately half of the world's population is infected with *H. pylori*; however, fewer than 3% of the infected individuals develop gastric cancer [6]. The occurrence of *H. pylori*-related gastric cancer not only depends on *H. pylori* infection, but also on the host's genetic susceptibility, which particularly involves genetic variants related to immune and inflammatory response [7]. Here, we review the role of host inflammatory gene variants in *H. pylori*-related gastric cancer.

Mechanisms by which *H. pylori* induces gastric cancer

H. pylori is a gram-negative, urease-positive, spiral-shaped bacillus that infects the gastric mucosa. *H. pylori* infection is one of the most common chronic bacterial infections in the world. Once acquired, the infection persists for decades in the gastric mucosa, triggering sophisticated, innate, and adaptive immune responses [8]. *H. pylori* can induce the activation of transcription factors that regulate cytokine gene expression. Cytokines produced during *H. pylori* infection, such as the interleukin (IL)-1β and tumor necrosis factor (TNF)-α, can regulate the physiological processes in the stomach, such as inhibiting gastric secretion and retarding gastric emptying [9]. *H. pylori*-induced inflammation is mediated by pro- and anti-inflammatory cytokines, which are produced to eliminate

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the invading pathogen and protect the host from pathogen-associated damage [10]. The development of atrophic gastritis, which is the most important stage in the development of *H. pylori*-induced gastric cancer, is related to the severity and extent of inflammation [11].

In addition, *H. pylori* is able to activate pro-inflammatory cyclooxygenase (COX) enzymes and phospholipase A2, which are catalysts in the key steps of the inflammatory pathway [12–13]. Sung *et al* found that COX-2 expression was increased in atrophic gastritis, intestinal metaplasia, and gastric cancer lesions in *H. pylori* infection, and that the eradication of *H. pylori* infection may lead to the reduction of COX-2 expression [14]. However, the changes in COX-2 expression are not associated with a progression of intestinal metaplasia. Another study found that the use of COX-inhibitors, such as aspirin and other non-steroidal anti-inflammatory drugs, could decrease the risk of gastric cancer [15]. *H. pylori* can induce the release of reactive oxygen and nitrogen species in the inflammatory response, which can cause damage to DNA and cause somatic mutations that promote oncogenesis [16]. Reactive oxygen species (ROSs) can produce single-stranded and double-stranded DNA breaks, which increase the risk of chromosome instabilities [17–18]. *H. pylori* can also induce gene methylation of multiple CpG islands, especially at the promoter sites relevant to the initiation and progression of gastric cancer [19]. While *H. pylori* is the main cause of gastric carcinogenesis, other causes include lifestyle, socioeconomic status, pernicious anemia, and host genetic variants.

Host inflammatory gene variants in *H. pylori*-related gastric cancer

The role of host inflammatory gene variants in *H. pylori*-related gastric cancer has been widely studied worldwide. Single nucleotide polymorphisms (SNPs) of inflammatory genes may affect gene transcription or splicing, leading to altered protein expression, and subsequently different immune responses against *H. pylori*. The following section describes the host gene variants related to immune and inflammatory responses that are associated with susceptibility to *H. pylori*-related gastric cancer.

IL-1

The *IL-1* gene family is located on chromosome 2, and encodes three cytokines: IL-1α, IL-1β, and the IL-1 receptor antagonist (IL-1ra) [20]. *H. pylori* infection can induce the upregulation of IL-1β, which induces and promotes *H. pylori*-associated inflammation [21]. IL-1β is a pro-inflammatory cytokine that inhibits gastric acid secretion [9]. Three polymorphisms (T-31C, C-511T, and T+3954C) of the *IL-1β* gene have been reported, all of which are located in the gene's promoter region. El-Omar *et al* found a significant association between the *IL-1B* gene polymorphisms, T-31C and C-511T, and the risk of *H. pylori*-associated gastric cancer, precancerous lesions, hypochlorhydria, and atrophic gastritis in the Caucasian population. In addition, this study determined that in the absence of *H. pylori* infection, individuals with mutant genotypes showed increased expression of IL-1β than those with wild genotypes [22]. This finding was supported by research that also identified another *IL-1β* locus, T+3954T, which is associated with an increased risk of gastric cancer [23–24]. Additionally, the *IL-1RN*2* polymorphism in the second intron of the *IL-1RN* gene, which encodes a variable number of tandem repeats, has been reported to be associated with an increased risk of chronic inflammation and autoimmune disease [22]. Meta-analysis revealed that *IL-1RN*2* can increase the risk of gastric cancer in Caucasians, but not in the Asian population [25].

IL-8

IL-8 belongs to the family of CXC chemokines, and it plays an important role in *H. pylori*-related diseases. IL-8 is induced by *H. pylori* infection and it affects cell proliferation, migration, and tumor angiogenesis. The gene polymorphism, *IL-8 –251T>A*, located in the promoter region of the *IL-8* gene, has a significant association with *H. pylori*-related gastric cancer. The adenine allele of the *IL-8 –251T>A* polymorphism is associated with an increased production of IL-8 by gastric mucosa cells infected with *H. pylori*, and significantly increases the risk of *H. pylori*-related atrophic gastritis and gastric cancer [26]. However, this finding has not been confirmed in some Caucasian and Asian populations [27–28]. These studies suggest that the effect of this genetic polymorphism on susceptibility to *H. pylori*-associated gastric cancer may have regional differences.

IL-10

IL-10 is an anti-inflammatory cytokine that can downregulate IL-1β, TNF-α, interferon-γ, and other pro-inflammatory cytokines. IL-10 production can decrease the extent of inflammatory damage to the gastric mucosa due to *H. pylori* infection. Three *IL-10* gene polymorphisms, *IL-10 –1082G*, *–592C*, and *–819C*, located in the promoter region, are associated with an increased risk of *H. pylori*-related gastric cancer [29–30]. Furthermore, El-Omar *et al* found that the combination of all three *IL-10* polymorphisms (*IL-10* ATA haplotype) further increased the risk of non-cardia cancer [31].

TNF-α

The pro-inflammatory cytokine, TNF-α, is produced in the gastric mucosa in response to *H. pylori* infection, and it inhibits the secretion of gastric acid, similar to IL-1β. The *TNF-α –308G>A* polymorphism is associated

with inflammatory disorders, and the adenine allele of the *TNF-α –308G>A* polymorphism increases the risk of non-cardia gastric cancer [32]. However, this association was not confirmed in some populations [33]. Another *TNF-α* polymorphism, *TNF-α –238*, has been associated with a significantly reduced risk of *H. pylori*-related gastric cancer [34]; however, this was not confirmed by other studies [29, 35].

Toll-like receptors

Toll-like receptors (TLRs) are signaling receptors that recognize lipopolysaccharides of *H. pylori*, and can initiate signal transduction pathways that trigger the expression of pro-inflammatory genes, such as *IL-1A*, *IL-1B*, *IL-8*, and TNF-α [36–37]. Arbour *et al* found that a functional SNP, *TLR4+ 896A>G* (rs4986790), located on the fourth exon of *TLR4*, can cause a missense mutation, from aspartic acid to glycine (Asp299Gly), resulting in the structural change of the *TLR4* receptor domain [38]. Hold *et al* found that for *H. pylori*-infected individuals, the *TLR4+ 896A>G* polymorphism was shown to be associated with non-cardia gastric carcinoma, as well as the associated precursor diseases, including gastric atrophy and hypochlorhydria [39]. In addition, another gene polymorphism, *TLR1 602S* (T1805G), was shown to be significantly associated with a reduced risk of *H. pylori*-related gastric ulcers and gastric cancer [40].

Inflammatory gene polymorphisms found in genome-wide association studies

Genome-wide association studies (GWAS) of gastric cancer have identified novel susceptibility loci, which have offered new molecular insights into gastric carcinogenesis [41–42]. Some SNPs identified in the GWAS are located on the genes related to inflammatory response. The Mucin1 (MUC1) protein is a receptor for *H. pylori*, which can limit the colonization of *H. pylori* and the inflammation caused by infection [43]. The *MUC1* SNP, rs4072037 (G>A), located on the second exon of *MUC1*, determines a splicing acceptor site in the signal peptide region. The GWAS reported that the variant allele guanine of rs4072037 was associated with a decreased risk of gastric cancer [41]. Furthermore, a multiplicative interaction has been found between *H. pylori* seropositivity and the gene variants of *MUC1* [44]. The guanine allele is associated with increased expression of the MUC1 protein in gastric cancer tissue [45]. In addition, it has been reported that mice deficient of *MUC1* are more susceptible to *H. pylori* gastritis [43]. Other gene polymorphisms located on inflammatory genes, such as rs13361707 and rs2274223, were identified in the GWAS to be associated with gastric cancer. However, the mechanisms by which these gene variants are associated with *H. pylori*-related gastric cancer is poorly understood.

Gastric cancer is an inflammation-related malignancy induced by infection, and develops after several decades in individuals with a genetic predisposition. Preventing *H. pylori* infection, or eradicating it before irreversible damage is established, is the most effective strategy to eliminate this cancer. Eradication of *H. pylori* infections may promote the resolution of inflammation, and may also reduce the risk of gastric cancer [46–47]. However, the possibility of reducing the risk of gastric carcinogenesis by *H. pylori* eradication depends on the level of gastric atrophic damage at the time when the *H. pylori* infection is cured. If the infection is cured at the stage of non-atrophic gastritis and metaplastic epithelia, then the risk of cancer is minimal. However, cancer risk remains in patients who have already developed atrophic gastritis, and the risk is associated with the extent and severity of atrophic changes [48–49]. In Japan, the guidelines for *H. pylori* management considered all *H. pylori*-infected patients as having a high risk of developing *H. pylori*-associated disorders, and that follow-up endoscopic surveillance was necessary for all infected individuals, even after the *H. pylori* infection had been cured [50].

Although an *H. pylori* infection will not induce obvious clinical symptoms in most people, it may lead to the development of serious diseases, such as gastric cancer. Gastric cancer is still a great threat to public health, with high incidences and a poor prognosis. Gastric carcinogenesis is a complex process that involves host gene polymorphisms, bacteria toxicity, and environmental factors. More research is needed to develop a more comprehensive understanding of the host gene mutations that are associated with susceptibility to *H. pylori*-related gastric cancer. This information will aid in our understanding of the pathogenesis of gastric cancer in order to prevent and eliminate further occurrences of *H. pylori*-related gastric cancer.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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