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REVIEW

Helicobacter pylori in gastric carcinogenesis

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Abstract

Gastric cancer still is a major concern as the third most common cancer worldwide, despite declining rates of incidence in many Western countries. *Helicobacter pylori* (*H. pylori*) is the major cause of gastric carcinogenesis, and its infection insults gastric mucosa leading to the occurrence of atrophic gastritis which progress to intestinal metaplasia, dysplasia, early gastric cancer, and advanced gastric cancer consequently. This review focuses on multiple factors including microbial virulence factors, host genetic factors, and environmental factors, which can heighten the chance of occurrence of gastric adenocarcinoma due to *H. pylori* infection. Bacterial virulence factors are key components in controlling the immune response associated with the induction of carcinogenesis, and *cag*A and *vac*A are the most well-known pathogenic factors. Host genetic polymorphisms contribute to regulating the inflammatory response to *H. pylori* and will become increasingly important with advancing techniques. Environmental factors such as high salt and smoking may also play a role in gastric carcinogenesis. It is important to understand the virulence factors, host genetic factors, and environmental factors interacting in the multistep process of gastric carcinogenesis. To conclude, prevention *via H. pylori* eradication and controlling environmental factors such as diet, smoking, and alcohol is an important strategy to avoid *H. pylori*-associated gastric carcinogenesis.

Key words: *Helicobacter pylori*; Gastric cancer

Core tip: *Helicobacter pylori* (*H. pylori*) is an important etiologic agent in gastric carcinogenesis. Here, we summarize not only recently investigated mechanisms of virulence factors, host genetic factors, and environmental factors, but also potential prevention. The best preventive methods in *H. pylori*-induced carcinogenesis may be achieved through *H. pylori* eradication, dietary, or lifestyle modifications, as well as a better understanding of molecular pathogenesis.

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INTRODUCTION

Gastric cancer remains the third leading cause of cancer death worldwide[1,2]. Although the incidence rates in the United States and many Western countries have declined significantly, the prevalence remains high in Eastern Europe, Central, and South America, and especially in East Asia, where up to 24.18 cases of gastric cancer per 100000 adults were estimated in 2012[3].

Because nearly 40% of patients never report tumor-related symptoms before diagnosis, most gastric cancer cases are advanced-type upon initial presentation, for which prognosis remains poor[4]. Thus, prevention may be the most promising strategy for cancer control.

Despite the fact that the molecular pathways of gastric carcinogenesis remain unclear[5], there are numerous factors that have been associated with gastric carcinogenesis, such as genetic background[6,7], behavioral factors (*e.g*., alcohol, smoking, diet)[8,9], and *Helicobacter pylori* (*H. pylori*). Most importantly, *H. pylori* is the most crucial etiologic agent for gastric adenocarcinoma[10,11], which is involved in 90% of all gastric malignancies[12].

Here, we review the recently investigated mechanisms of *H. pylori*-induced gastric carcinogenesis, focusing not only on epidemiological factors, bacterial virulence factors, host factors, or other environmental factors, but also on preventive management and future directions.

H. pylori as a major risk factor for gastric cancer

H. pylori is a gram-negative microaerophilic bacterium that infects nearly 50% of the world's population. It has been found in every population premeditated, although the incidence varies with age, childhood socio-economic status, education level, living environment, occupation, and geographic regions, in that the incidence is higher in developing countries and much of East Asia[13-15].

In 1994, *H. pylori* was categorized as a class I (definite) carcinogen by the International Agency for Research on Cancer (IARC), a division of the World Health Organization (WHO)[15,16]. Subsequently, it is believed that *H. pylori* is the major risk factor of gastric cancer based on animal studies[17,18], as well as clinical observational and human interventional studies[10,19-21].

The clinical manifestations of *H. pylori* infection are as follows: (1) chronic gastritis, which almost all patients develop and most remain asymptomatic; (2) duodenal ulcer (DU) phenotype, which occurs in 10%-15% of infected individuals; (3) gastric ulcer/adenocarcinoma phenotype, which develops into gastric cancer in 1%-3% of infected individuals; and (4) gastric mucosa–associated lymphoid tissue lymphoma (MALToma), which develops in 0.1% of infected subjects[12,15,22,23]. The DU phenotype with antral colonization is associated with high gastrin and high output of gastric acid, and also related to a lowered risk for gastric cancer occurrence[15,20,24]. However, the gastric adenocarcinoma phenotype, which occurs more frequently when there is proximal colonization of the stomach (pangastritis), brings about damage to gastric glands, causing atrophic gastritis and associated hydrochlorhydria or achlorhydria, and it is characterized by low pepsinogen I and high gastrin levels and a low pepsinogen I/II ratio. This phenotype eventually progresses to a multistep process including intestinal metaplasia, dysplasia, and adenocarcinoma[20,23-25]. This series of histological changes may take as long as 7 or 8 decades[26] and is a well-known characteristic of intestinal-type adenocarcinoma, which is one of two distinct histological variants. It is also believed that *H. pylori* is associated with diffuse-type adenocarcinoma[11], which shows the paucity of glandular structure and comprises poorly cohesive cells that infiltrate the gastric wall[15]. However, pathological sequences of the diffuse-type are less characterized[26].

Gastric adenocarcinoma is also categorized into proximal tumors (esophagogastric junction and gastric cardia) and distal tumors (gastric antrum, body, and fundus)[15]. Proximal gastric cancers have different epidemiological and pathophysiological characteristics compared with distal cancer, and many studies support that this type of cancer is inversely associated with *H. pylori* infection[21,27,28] despite some debates[29,30]. Although the incidence of cancer of the proximal stomach has been increasing, the majority of gastric cancers worldwide arise from the distal stomach, and the significance of *H. pylori* in gastric carcinogenesis remains overwhelming.

PATHOGENESIS OF *H. PYLORI* IN GASTRIC CARCINOGENESIS

As mentioned above, *H. pylori*-induced gastric carcinogenesis in humans rarely occurs among infected individuals. Many studies over the past three decades suggest that the combination of a bacterial virulent strain, a genetically susceptible host, and a predisposed gastric environment may be required for cancer to develop.

Bacterial virulence factors

H. pylori yields various virulence factors that may dysregulate host intracellular signaling pathways and decrease the threshold for neoplastic transformation. Of all virulence factors, *cag*A (cytotoxin-associated gene A) and its pathogenicity island (*cag* PAI) and *vac*A (vacuolating cytotoxin A) are the major pathogenic factors.

***Cag* PAI and *cag*A:** The most well-featured *H. pylori* virulence factor is the *cag* PAI, which is about 40 kb and contains 27-31 genes. The terminal gene of this island, *cag*A, is a highly immunogenic protein often used as a indicator for the entire *cag* PAI locus[26]. It is believed that *cag*A-positive (*i.e.*, *cag* PAI-positive) strains are

linked to more harsh inflammation, higher steps of atrophy, and a larger possibility of advancement to adenocarcinoma of stomach compared with *cag*A-negative (*i.e., cag* PAI-negative) strains[15,31-34]. The estimated relative risk (RR) ranges from 2 to as high as 28.4[23]. However, the same clinical diseases of these are also originated by infections with *cag*A-negative strains, compatible with the assumption that any other bacterial or host factor may contribute to increased risk of a significant clinical outcome[35].

The prevalence of *cag*A differs widely according to region. It varies dramatically, with the prevalence reaching almost 100% in East Asia, and less than 50% in some countries in the West[36]. It has been observed that people with *cag*A-positive strains of *H. pylori* are more susceptible to peptic ulcer disease or gastric adenocarcinoma than are those with *cag*A-negative strains in Western countries[37,38]. In East Asia, most *H. pylori* strains possess the *cag*A gene without regard to the disease; therefore, the pathogenic difference in East Asia is hard to explain concerning the existence of the *cag*A gene alone[39]. Thus, the combined circumstances that permit *cag*A to initiate carcinogenesis remain unclear.

The *cag* PAI encodes a type Ⅳ secretion system (T4SS; *i.e.*, a molecular motors) that injects at least 18 proteins including *cag*A into host cells[14,40].

***Cag*A and glutamate-proline-isoleucine-tyrosine-alanine motifs:** The *H. pylori cag*A protein is a 120- to 140-kDa protein translocated into host cells by the T4SS after bacterial attachment. When the cagA enters the host cell, it can bind to the cell membrane inner surface and undergo tyrosine phosphorylation. This in turn results in morphological changes of the cell, and influences various intracellular signal transduction pathways. In addition, *cag*A exerts pathogenic effects without phosphorylation. Both the phosphorylation-dependent and -independent *cag*A signals interact with many host proteins to trigger downstream pathways, such as the ras/mitogen-activated protein kinase/extracellular signal-regulated kinase pathway[41,42], nuclear factor κB (NF-κB) pathway and B-catenin pathway[43].

Glutamate-proline-isoleucine-tyrosine-alanine (EPIYA) motifs are the sites of *cag*A phosphorylation. According to variations in the encompassing amino acid sequence, four distinct EPIYA-motifs are reported (-A, -B, -C, -D)[44,45]. The first repeat region comprises EPIYA-A/EPIYA-B segments and is present in strains throughout the world. However, the prevalence of the second repeat region varies by geographic area. The respective names of the second repeat region segments of the Western and East Asian strains are EPIYA-C and EPIYA-D[35,46]. In Western strains, an increased number of *cag*A EPIYA-C sites is an significant barometer of the risk of progressing to gastric adenocarcinoma[47]. East Asian strains are nearly the only strains to carry the EPIYA-D motif. These are strains from South Korea, Japan, and China. Many studies have concluded that when infections that occur in the same area are compared, infection with EPIYA-D strains have a higher risk of gastric cancer or peptic ulcer compared to infection with EPIYA-C strains[35,48-50]. However, the role of *cag*A remains unclear. In some reports, *cag*A can micro-evolve within an individual[51] or the EPIYA-B motif may be polymorphic[52]. Thus, further studies are required to explore the association between *cag*A EPIYA motifs and gastric carcinogenesis.

***Vac*A:** All strains of *H. pylori* possess and more than half express the *vac*A gene, which encodes a pore-forming protein that binds to epithelium *via* interaction with protein-tyrosine phosphatases[53]. *vac*A protein is a very potent inhibitor of T cell activation *in vitro*[54], and it has multiple activities, such as pore-formation in membranes, cytochrome C release from mitochondria progressing to apoptosis, and attaching to cell membrane receptors resulting in pro-inflammatory responses[36].

There are many studies showing that differences in *vacA* gene structure are associated with severities of clinical disease. According to variations in *in vitro* vacuolating capacity, studies have reported differences in the signal region (s1 and s2), the middle regions (m1 and m2), and recently the intermediate regions (i1 and i2)[47,55,56]. Investigators have suggested that when compared to s2 or m2 strains, individuals who have been infected with *vac*A s1 or m1 strains may have a heightened risk of gastric cancer and/or peptic ulcers in Africa, Latin America, and the Middle East[57,58]. More recently, i1 strains have been suggested to be correlated not only with inflammatory and dysplastic, but also malignant neoplastic tissue formation in Portugal, Belgium, and Iran[59-61]. However, unlike the above reports, in a reports of subjects from East and Southeast Asia, there was no correlation between the i-region and clinical disease[36]. In a recent long-term study (mean 12.8-year follow-up) based on Spanish populations, there was no correlation between the i-region and clinical outcome either[62]. In addition, there are relatively few studies that have controlled for variables associated with inflammation severity, such as the presence of *cag*A. In summary, despite numerous reports that the *vac*A s1/i1 genotypes are highly pathogenic, no clear association has been observed yet.

Host genetic factors

There is increasing evidence that the nature of the inflammatory response to *H. pylori* is in large part determined by polymorphisms in several host genes encoding cytokines and cytokine receptors.

***IL-1* gene cluster polymorphism:** El-Omar *et al*[63] first reported that pro-inflammatory *IL-1* gene cluster polymorphisms (*IL-1B* gene encoding cytokine *IL-1β* and *IL-IRN* gene encoding its naturally occurring receptor antagonist, IL-1RA) were clearly related

to an intense inflammatory response resulting in hypochlorhydria and high risk of cancer. Subjects with the IL-1B-31*C or -511*T and IL-1RN*2/*2 genotypes have a higher risk of gastric atrophy, gastric cancer, or hypochlorhydria as a result of *H.pylori* infection[23,63,64]. The heightened risk of cancer development with these genotypes was 2- to 3-fold compared with non-inflammatory genotypes[63-65]. These findings have been confirmed in other groups such as Caucasian, Hispanic, and Asian populations[65-71].

In addition, Figueiredo *et al*[66] analyzed the mutual effects of bacterial virulence factors of *H. pylori* (*cag*A-positive, *vac*A s1, and *vac*A m1) and proinflammatory IL-1 genotypes. They showed that pro-inflammatory polymorphisms of IL-1, together with carriage of *H. pylori* with the *vac*A s1 form, heightened the possibility of developing gastric cancer 87-fold compared with individuals who had neither of these risk factors yet were still colonized by *H. pylori*[66]. Crucial evidence, provided by a transgenic study, has confirmed the exclusive role of IL-1β in *H. pylori*-associated gastric carcinogenesis[72]. According to this study, in transgenic mice, human IL-1β stomach-specific expression resulted in gastric cancer and spontaneous gastric inflammation which were associated with early recruitment of myeloid-derived suppressor cells to the stomach.

Despite some conflicting results among Caucasian, Asian, and Hispanic populations, there is a consensus that IL-1B and IL-IRN are crucial cytokine receptors in the pathogenesis of *H. pylori*-induced gastric carcinogenesis[73-76].

Other cytokine gene polymorphism: Additional relations with gastric cancer risk for genetic polymorphisms in TNF-α and IL-10 have been reported[64]. Pro-inflammatory genotypes of TNF-α and IL-10 were each related to an approximately two-fold greater possibility of nocardia gastric cancer[64,65]. Additional reports have suggested that polymorphisms of the Toll-like receptor-4 (*TLR-4*) gene also heightens gastric cancer risk. An 11-fold increase in the odds ratio (OR) for hypochlorhydria was found in the TLR4 + 896G polymorphism carriers. Also, in Caucasian populations, these carriers had significantly more severe atrophic gastritis and inflammation[77].

Host genetics and gastric cancer in the era of Genome Wide Association Studies and future perspectives: In 2008, Sakamoto *et al*[78] first reported that an intronic single nucleotide polymorphism (SNP; rs2976392) in the prostate stem cell antigen (PSCA) was significantly associated with diffuse-type gastric cancer in Japan. Recent two meta-analyses also suggested that PSCA -rs2294008C>T and -rs2976392G>A were potential factors of gastric cancer development in East Asians[79,80]. In addition, it has been thought that the PSCA-rs2294008 polymorphism heightened risk of non-cardiac gastric cancer but protects against proximal cancer in Caucasian populations[81,82]. With recent advances in technology, we can increase our understanding of the genetic mechanisms of gastric carcinogenesis through SNP and next generation sequencing, which could be useful for screening and a necessary step for more effective treatment.

Environmental factors

Environmental factors may also play a role in *H. pylori*-induced gastric carcinogenesis. Salt is a well-known dietary factor. In a Japanese prospective study in 2006[83], a significant correlation between salt consumption and gastric adenocarcinoma was reported in individuals who had both *H. pylori* infection and atrophic gastritis [age- and sex-adjusted hazard ratio, 2.87 (1.14-7.24)]. In addition, according to a recent animal study, high dietary salt intake potentiates the carcinogenic effects of *cag*A-positive *H. pylori* strains[84]. There are some suggestions on the mechanisms by which salt potentiates *H. pylori*-induced gastric carcinogenesis; however, they are not entirely understood. First, salt may destroy the gastric mucosa, thereby leading to inflammation and damage or permitting entry of carcinogens into stomach[14,85]. Second, upregulated production of proinflammatory enzymes and cytokines such as nitric oxide synthase and cyclooxygenase-2 (COX-2) in response to a high-salt consumption may be contributing[86]. Finally, recent reports suggest that high salt concentrations modulate virulence factors, including *cag*A, in *H. pylori*[87,88].

Smoking may be the most significant lifestyle-related risk factor. In a recent systemic review and meta-analysis of cohort studies, it was shown that smoking is correlated with an high relative risk for both gastric cardia [1.87 (1.31-2.67)] and non-cardia cancers [1.60 (1.41-1.80)] significantly[89].

Other factor: Ancestral origin

H. pylori can be divided into seven global populations and subpopulations with distinct geographic distributions, genetically derived from ancestral populations such as those in Africa (Ancestral Africa 1 or 2; AA1 or 2), Europe (Ancestral Europe 1 or 2; AE1 or 2), and East Asia (Ancestral East Asia; AEA). While stomach cancer rates correlate with *H. pylori* prevalence in some areas, in other regions there is no correlation with *H. pylori* prevalence, such as some regions in Africa or South America[90]. In Columbia, the reported gastric cancer rate in the Andes Mountains (approximately 150 per 100000) is 25-fold higher than that in coastal regions (approximately 6 per 100000), in spite of similarly high (approximately 90%) prevalences of *H. pylori* in the two regions[2]. As recently reported[91] in those populations, the authors extracted both human ancestry, from the participants' DNA, and *H. pylori* ancestry, from antral biopsies of the participants, and assessed how coevolution may have had on effect on gastric disease. Remarkably, they found that the interaction between Amerindian host ancestry and *H. pylori* ancestry AA1, which affects the severity of premalignant histopa-

thology, was approximately five-fold larger than the effect of *cag*A (RR = 5.08 *vs* 0.98). This result suggested that ancestral coevolutionary relationships can be significant determinants of gastric cancer.

PREVENTION

The most important primary prevention strategies for gastric cancer potentially include behavioral (dietary or lifestyle) modifications and a decline in the prevalence of *H. pylori*, the major causal factor of gastric cancer[92]. Although the pathogenesis remains unclear, prevention through dietary intervention would include increased fruit, allium, and non-starchy vegetable intake and reduced ingestion of salt or salt-preserved foods and N-nitroso compounds[93-98]. Lifestyle modifications such as maintaining normal weight, limiting alcohol consumption, and smoking cessation may also lower the risk of the disease[99].

H. pylori eradication as a preventative measure for gastric carcinogenesis

H. pylori eradication may be the most efficient method to prevent gastric cancer, in that *H. pylori* infection can persist for decades and slowly progress from preneoplastic lesions to gastric cancer. It is believed that *H. pylori* eradication can suppress the recurrence of peptic ulcers, induce remission of MALToma of the stomach, and lower the rate of recurrence after endoscopic resection of early gastric cancer. However, demonstrating that *H. pylori* eradication directly decreases gastric cancer risk remains challenging.

Currently, a novel meta-analysis of six randomized trials performed in asymptomatic adults estimated a benefit from *H. pylori* eradication (RR = 0.66; 95%CI: 0.46-0.95)[100]. A Chinese randomized controlled trial performed in 2012 in the general adult population concluded that there was a significant decline of gastric cancer risk after 15 years of follow-up (4.6% in the control group, 3.0% in the treated group; OR = 0.61; 95%CI: 0.38-0.96)[101]. Despite some limitations of the study, such as examination of middle-aged groups only and a relative paucity of endpoint data, these well-designed studies have presented good results in terms of eradication therapy for prevention of gastric cancer. In addition, a recently published report from the WHO's IARC, conducted in a working group population, concluded that *H. pylori* eradication can be efficient in gastric cancer prevention, and *H. pylori* screening and treatment strategies would be cost-effective. However, uncertainties regarding the generalizability of the results, cost-effectiveness, and possible adverse outcomes of programs applied in community settings need to be explored[92].

Recent changes in H. pylori eradication subjects

Peptic ulcer, MALToma, and endoscopic treatment of early gastric cancer are well-known indications for *H. pylori* eradication. Recently, it is generally acknowledged that iron deficiency anemia, idiopathic thrombocytopenic purpura, functional dyspepsia, and long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) or proton pump inhibitors (PPIs) are considered highly evident indications[102-106]. In the context described above, Japanese guidelines revised in 2009 strongly recommend (Recommendation grade A) that all *H. pylori* infections should be eradicated regardless of the associated disease[106]. In addition, in the Kyoto Global Consensus Meeting on *H. pylori* Gastritis (From January 30, 2014 to February 1, 2014), it was suggested by 46 authorities that all *H. pylori*-infected individuals, including asymptomatic individuals, should be considered eradication subjects, especially in those with functional dyspepsia[107,108]. Thus, in other East Asian countries such as South Korea and China, where the prevalence of *H. pylori* infection and gastric cancer remains high, careful consideration is required for eradication therapy.

Recent trends in the H. pylori eradication regimens and antibiotics resistances

Although standard triple therapy (PPI + clarithromycin + amoxicillin or PPI + clarithromycin + metronidazole) is still recommended as a first-line regimen in recent Korean and Japanese guidelines[104-106], the increasing rate of eradication failure due to primary resistance to clarithromycin and metronidazole is a global concern[109-111]. Recently, high (≥ 20%) resistance rates of clarithromycin have been reported in the United States and developed countries in Europe and Asia, while relatively low (< 10%) rates have been reported in North Europe[112,113]. Especially, one Japanese multicenter study reported that clarithromycin-resistance rates have increased rapidly from 18.9% in 2002 to 27.2% in 2006[114]. In addition, over 80% of metronidazole-resistance rates have been observed in Africa, Iran, and South America, and 20%-40% of metronidazole-resistance rates have also been reported in United States, Europe, and East Asia[112,115]. Primary quinolone-resistance rates have also been increasing (> 10%) in developed countries in Europe and Asia[112,115,116]. Besides, amoxicillin resistance in Europe has been very low (0% to < 2%) but higher (6%-59%) in Asia, South America, and Africa, and tetracycline resistance has been low or absent (< 5%) in most countries while higher (9%-27%) in South America and Asia[112,115].

With regard to the high resistance to clarithromycin, recent European guidelines[102] recommend that first-line regimens should be tailored according to clarithromycin resistance. In low-resistance (< 20%) regions, standard triple therapy is recommended as a first-line regimen, while in high-resistance (> 20%) regions, bismuth quadruple therapy or sequential/concomitant therapy is recommended first. However, in East Asia, we could not evaluate the superiority of sequential/concomitant therapy over standard therapy[103,104,106,117].

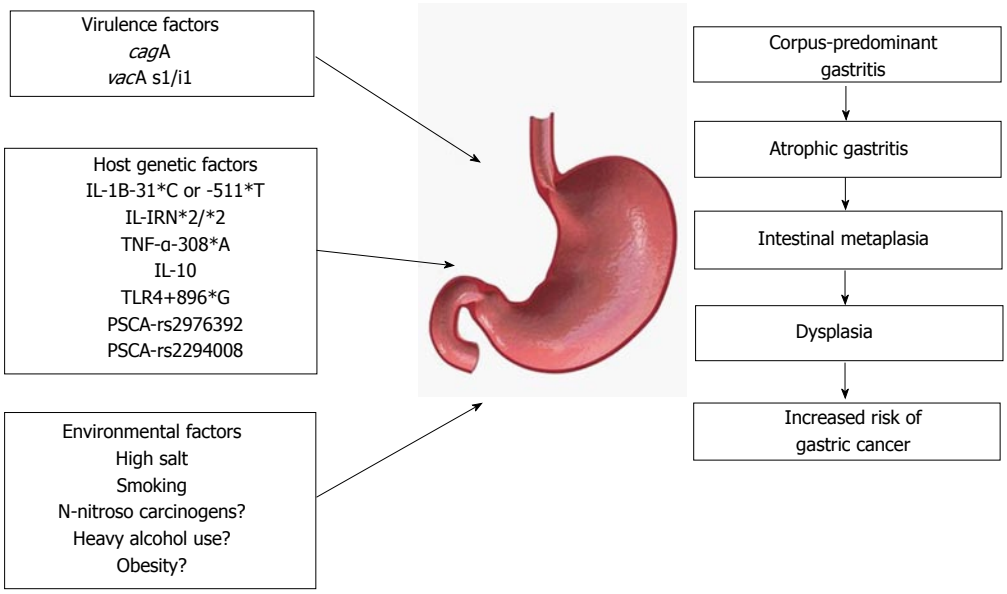

Figure 1 Multiple factors related to *helicobacter pylori*-induced gastric carcinogenesis. IL: Interleukin; TNF: Tumor necrosis factor; TLR-4: Toll-like receptor-4; PSCA: Prostate stem cell antigen.

Thus, to maximize the *H. pylori* eradication treatment effect, individually tailored treatment with consideration of a variety of demographic factors including genetic polymorphisms, antibiotic resistance, and age will be important in the future.

Other protective agents against H. pylori-associated gastric carcinogenesis

The role of aspirin, NSAIDs, and COX-2 inhibitors in gastric carcinogenesis should be considered, because *H. pylori* infection is thought to induce COX-2 overexpression[118,119], and higher levels of COX-2 expression have been observed in gastric carcinoma and premalignant lesions[120,121]. Therefore, it is believed that intervention with aspirin, NSAIDs, and COX-2 inhibitors inhibits or reverses the process of *H. pylori*-related carcinogenesis and prevents the development of gastric cancer[122].

Vitamin C and antioxidants are also considered protective against *H. pylori*-induced gastric carcinogenesis by strengthening the mucosal immune response, neutralizing free radicals, reducing the creation of gastric N-nitroso compounds, inhibiting cell proliferation, and directly influencing *H. pylori* growth[92]. According to a recent meta-analysis of randomized trials conducted in asymptomatic adults, *H. pylori* eradication in combination with antioxidants or vitamins showed a beneficial impact (RR = 0.52; 95%CI: 0.31-0.87)[100]. However, to date, there have been conflicting data in association with gastric cancer and NSAIDs or vitamin C; thus, further studies are required to support the roles of these agents in *H. pylori*-associated gastric carcinogenesis.

In addition, in a recent meta-analysis based on 45 randomized controlled trials, the additional use of probiotics with standard triple therapy was associated with an increased *H. pylori* eradication rate in the per-protocol set (OR = 1.13; 95%CI: 1.10-1.16), a reduction in adverse events (RR = 0.59; 95%CI: 0.48-0.71), and economic burden and a poor compliance rate[123].

FUTURE DIRECTIONS AND CONCLUSION

H. pylori infection is major factor for gastric carcinogenesis. During *H. pylori* infection and subsequent inflammation and carcinogenesis over a time span of decades, numerous factors including bacterial virulence, host genetic, and environmental factors interact and elicit variable clinical outcomes (Figure 1). Thus, understanding the complex mechanisms of a variety of factors is important and may provide future directions for novel therapy.

To date, prevention throughout behavioral management and *H. pylori* eradication may be an important strategy to reduce the occurrence of gastric cancer. A unique contrivance on potential dietary or other chemopreventive agents and related well-designed studies are required. In addition, it is important to take into account whom to eradicate, when to eradicate, and what regimen to use to eradicate *H. pylori* in the general population.

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