Helicobacter pylori Induces Hypermethylation of CpG Islands Through Upregulation of DNA Methyltransferase: Possible Involvement of Reactive Oxygen/Nitrogen Species

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Helicobacter pylori infection has been considered to be one of the major factors implicated in etiology of gastric cancer. Aberrant DNA methylation accounts for epigenetic modifications induced by H. pylori. H. pylori-induced hypermethylation has been linked to enhancement of the rates of metastasis and recurrence in gastric cancer patients. H. pylori-induced gene hypermethylation has been known to be associated with inflammation. However, the molecular mechanisms underlying H. pylori-induced hypermethylation remain largely unknown. This review highlights possible involvement of reactive oxygen/nitrogen species in H. pylori-induced hypermethylation and gastric carcinogenesis.

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Key Words: Helicobacter pylori, Hypermethylation, Reactive oxygen species, Reactive nitrogen species, Gastric cancer

INTRODUCTION

Gastric cancer is one of the most common malignancies in the world. Although the incidence of gastric cancer is declining, its prognosis remains poor. The etiology of gastric cancer is multifactorial which includes Epstein Barr virus, Helicobacter pylori, family history, diet, etc. The molecular mechanisms underlying gastric carcinogenesis involves both genetic and epigenetics differences. Besides accumulation of mutations in oncogenes and tumor suppressor genes, epigenetic alterations, such as methylation of cytosines of DNA, modification of histone, chromatin remodeling, and changes in the expression of microRNAs in cancer-related molecules, have been known to contribute to the premalignant manifestation of the gastric mucosa and finally gastric neoplasia. Environmental factors, such as aging, diet, chronic inflammation, and microbial infection, have been known to modulate the initiation and maintenance of epigenetic modifications. Epigenetic changes may be transmitted to the next generation, but can be reversed. Therefore, controlling abnormal epigenetic alterations provides opportunities for treatment or prevention of cancer.

Aberrant DNA methylation is one of the most prevalent epigenetic changes, which usually takes place at the 5' position of the cytosine ring within CpG dinucleotides, and its consequence is the silencing of genes and noncoding genomic regions. The modification at 5-methyl cytosine is catalyzed by a group of enzymes termed DNA methyltransferases (DNMTs). There are three main isoforms of DNMTs: DNMT1, which maintains the existing methylation patterns following DNA replication, DNMT3A, and DNMT3B that target unmethylated CpGs to initiate methylation. Overexpression of DNMT1, DNMT3A, and DNMT3B was observed in gastric cancer tissues. Moreover, co-expression of DNMT1 and DNMT3A was significantly associated with lymph node metastasis. It has been reported that
the genetic variations in the DNMT3A1 promoter contribute to the susceptibility to gastric cancer.\(^\text{11}\)

Approximately 400 genes that are actively expressed in normal gastric epithelial cells are estimated to be inactivated in gastric cancers as a result of hypermethylation of the CpG island present in their promoters.\(^\text{12}\) Methylation in tumor suppressor genes and those encoding molecules involved in regulating cell cycle, cell adherent/invasion/migration, cell growth, apoptosis, etc., is one of the most well-defined epigenetic alterations implicated in gastric carcinogenesis.\(^\text{13}\) Aberrant CpG island hypermethylation occurs early in the multi-stage gastric carcinogenesis and tends to increase with the step-wise progression of the malignancy.\(^\text{14}\)

Therefore, any insightful understanding of aberrant methylation and subsequent gene silencing is essential for cancer prediction, prevention, treatment, and prognosis.

\(H.\) pylori infection has been known to cause gastric carcinogenesis. \(H.\) pylori-induced gastric carcinogenesis has been associated with chronic inflammation, accumulation of reactive oxygen/nitrogen species (ROS/RNS) with subsequent oxidative/nitrosative DNA damage, silencing of tumor suppressor genes via epigenetic modification,\(^\text{15}\) and epithelial-mesenchymal transition.\(^\text{16}\)

However, the molecular mechanisms underlying aberrant gene methylation implicated in \(H.\) pylori-induced gastritis and gastric carcinogenesis are not yet fully understood.

**HELICOBACTER PYLORI-INDUCED ABERRANT METHYLATION IN THE PROMOTER OF GENES IS INVOLVED IN GASTRIC CARCINOGENESIS**

\(H.\) pylori infection has been reported to enhance aberrant DNA methylation in gastric mucosa, which contributes to increases in the gastric cancer risk.\(^\text{17,18}\) The rates of metastasis and recurrence were found to be higher in \(H.\) pylori positive cancer patients with aberrant DNA methylation than those without DNA methylation.\(^\text{19}\)

Eradication of the \(H.\) pylori infection was found to decrease overall methylation levels in patients with gastritis.\(^\text{20}\) \(H.\) pylori-related methylation alters not only the function of common oncogenes or tumor suppressor genes but also other genes involved in cell growth and differentiation.\(^\text{14,21,22}\)

For example, E-cadherin, a cell adhesion molecule responsible for maintaining the epithelial phenotype, is regarded as an invasion-suppressor gene.\(^\text{23}\)

Methylation of E-cadherin gene occurred in \(H.\) pylori-infected non-neoplastic gastric mucosa and gastric carcinoma particularly in poorly differentiated adenocarcinoma.\(^\text{24}\)

Methylation of E-cadherin can be reversed following \(H.\) pylori eradication.\(^\text{24}\) CagA, a virulence factor produced by \(H.\) pylori, has been known to be involved in methylation of some tumor suppressor genes. \(H.\) pylori strains expressing high levels of CagA more strongly suppressed expression of p53 compared with low-risk strains.\(^\text{25}\)

p53 degradation is prevented by the human tumor-suppressor protein p14ARF by binding to the MDM2-p53 complex.\(^\text{26}\) CagA has been shown to decrease the accumulation of p14ARF by hypermethylation or deletion of the gene encoding this tumor suppressor.\(^\text{25}\)

As a consequence, CagA induces degradation of p53 via hypermethylation of p14ARF.\(^\text{25}\)

The transcription factor forkhead box d3 (FOXD3) plays a key role in early embryonic development and is considered to be a novel tumor suppressor.\(^\text{27}\)

Knockdown of FOXD3 promoted the growth, migration, invasion and angiogenesis in various cancers.\(^\text{28}\)

FOXD3 methylation was found to be increased in gastric tissues from patients with \(H.\) pylori-positive gastritis compared with uninfected normal individuals.\(^\text{14}\)

In addition, FOXD3 promoter methylation was significantly elevated to a similar degree in intestinal metaplasia, but further increased in gastric cancer.\(^\text{14}\)

Moreover, expression of proapoptotic genes CYFIP2 and RARB, down-stream target molecules of FOXD3, was also suppressed in the gastric specimens.\(^\text{14}\)

Therefore, down-regulation of FOXD3 via \(H.\) pylori-mediated hypermethylation interrupts the balance between cell death and survival.\(^\text{14}\)

**HELICOBACTER PYLORI-INDUCED GENE HYPERMETHYLATION IS ASSOCIATED WITH INFLAMMATION**

Chronic inflammation is a well known factor responsible for promotion of many cancers. Approximately 15% to 20% of all human malignancies are related to chronic inflammation.\(^\text{29}\)

Gastric cancer is a typical inflammation-associated malignancy, being closely linked to \(H.\) pylori-induced chronic inflammation in gastric mucosa. Chronic inflammation caused by \(H.\) pylori infection is suggested to be an inducer of aberrant DNA methylation.\(^\text{30}\)

Expression levels of several inflammation-related genes (e.g., CXCL2, interleukin [IL]-1β, nitric oxide synthase 2, and tumor necrosis factor-α) correlate with the temporal changes in the methylation levels.\(^\text{30}\)

Inflammation induced by \(H.\) pylori infection is associated with enhancement of nitric oxide (NO)/inducible nitric oxide synthase (iNOS) expression via IL-1β production. A prototypic proinflammatory cytokine IL-1β induced hypermethylation of E-cadherin promoter.\(^\text{31}\)

\(H.\) pylori induced E-cadherin methylation is mediated through induction of IL-1β production.\(^\text{31}\)

In addition, IL-1β stimulates promoter methylation of anti-
inflammatory cytokine transforming growth factor-β1 (TGF-β1) in the human gastric epithelial cells. Methylation of TGF-β1 promoter is higher in H. pylori-positive gastric mucosal tissues than those without H. pylori infection. TGF-β1 promoter methylation is also increased in gastric cancer tissues. In addition, an immunosuppressive drug cyclosporin A exerts anti-proliferative activities in gastric and colon carcinoma cell lines. Cyclosporin A significantly suppressed inflammation as well as attenuated altered DNA methylation in H. pylori-infected gerbils, but did not affect colonization of H. pylori.

Generation of NO by iNOS induction is a common strategy exploited by the host to fight H. pylori infection. H. pylori infection stimulates expression of iNOS in the invading macrophages as well as in the gastric mucosa. H. pylori-induced DNA methylation is mediated by NO. H. pylori elevated the activity of DNMT and induced the expression of DNMT1 and DNMT3A in gastrointestinal stromal tumor. The iNOS inhibitor, Nω-nitro-L-arginine methyl ester, suppressed the NO production and DNMT activity caused by H. pylori infection. H. pylori did not increase DNA methylation in gastric cancer cells in the absence of macrophages, suggesting that induction of DNA methylation might be mediated by NO produced during inflammation. Therefore, inflammation driven by H. pylori infection contributes to hypermethylation of genes encoding tumor suppressor proteins and anti-inflammatory cytokines by generation of NO. Some anti-inflammatory agents may act as demethylating agents, thereby exerting anti-inflammatory and anti-carcinogenic activities.

**GENERATION OF REACTIVE OXYGEN/NITROGEN SPECIES BY HELICOBACTER PYLORI INFECTION IS INVOLVED IN THE METHYLATION OF ANTIOXIDANT ENZYMES**

One of the mechanisms underlying H. pylori-induced gastric injury is production of ROS by infiltrating neutrophils in the infected tissues. H. pylori-driven inflammation can produce ROS, which may lead to methylation of CpG islands in gene of methylation located on gene promoters. Disruption of a defence mechanism against oxidative stress leads to enhancement of ROS accumulation, which can initiate or promote carcinogenesis. Antioxidant enzymes such as catalase, superoxide dismutase, heme oxygenase-1, NAD(P)H: quinone oxidoreductase-1, and those involved in glutathione (GSH) metabolism play a key role in protecting cells against oxidative stress. Prolonged exposure to ROS decreased the expression of antioxidant enzymes such as Cu/Zn superoxide dismutase or catalase. H2O2 treatment induced methylation of CpG island II in the promoter of catalase and simultaneously down-regulated its expression and activity in hepatocellular carcinoma cell lines. Activity of catalase was significantly lower in adenocarcinoma and H. pylori-positive gastritis tissues.

Glutathione peroxidase 3 (GPX3) catalyzes the inactivation/neutralization of hydrogen peroxide and lipid peroxides by reduced GSH. Down-regulation or silencing of GPX3 via promoter hypermethylation was observed in some gastric cancer cell lines and gastric cancers specimens, as compared to adjacent normal gastric tissues. In addition, loss of GPX1 expression and its promoter methylation were closely associated with advanced gastric cancer development and lymphatic invasion. These findings suggest that there is a vicious cycle between ROS and low levels of antioxidant enzymes. Down-regulation of antioxidant enzymes enhances the generation of ROS and subsequently triggers aberrant methylation of CpG islands located in the promoter regions of antioxidant enzymes (Fig. 1).

Nuclear factor-erythroid 2-related factor 2 gene (Nrf2), a master regulator of many critical anti-oxidative stress defense genes, has been known to be inactivated through promoter CpG methylation/histone modifications. Heat shock protein B reduced Nrf2 gene accumulation and expression of superoxide dismutase, heme oxygenase-1, and NAD(P)H: quinone oxidoreductase-1 via upregulation of Keap1 expression. In addition, promoter polymorphisms of nrf2 gene has been known to affect the methylation status of the p14 tumor suppressor gene, under the influence of H. pylori-induced gastric inflammation. The Nrf2-686/-684 G/G haplotype was positively associated and A/G...
haplotype was inversely associated with the development of CpG island methylation, especially in the p14 gene methylation in non-cancerous gastric mucosa. In *H. pylori* infected subjects, the number of -686/-684 G/G allele was positively correlated and that of A/G allele was inversely correlated to status of the p14 methylation. Therefore, promoter polymorphisms of miR2 gene lead to down-regulation of p14 via methylation which may fail to suppress MDM2, and thereby promotes transcription of genes involved in cell cycle progression.

**HELICOBACTER PYLORI INFECTION INDUCES METHYLATION OF microRNAs (miRNAs)**

Recently, accumulating data suggest that some miRNA can function as oncogenes or tumor suppressors. Silencing of some miRNAs in tumors is associated with CpG island hypermethylation. Sixteen miRNAs were upregulated in gastric carcinoma. These include miR-223, miR-21, miR-23b, miR-222, miR-25, miR-23a, miR-221, miR-107, miR-103, miR-99a, miR-100, miR-125b, miR-92, miR-140a, miR-214, and miR-191. In contrast, six miRNAs including let-7a, miR-126, miR-210, miR-181b, miR-197, and miR-30aa-5p were down-regulated in gastric carcinoma. Expression levels of several miRNAs, such as miR-210, miR-375 and miR-99a, were found to be reduced in the gastric epithelium of Mongolian gerbils infected with *H. pylori* as compared with those in uninfected gerbils. Among these, DNA methylation of the miR-210 gene is increased in *H. pylori*-positive human gastric biopsies as compared with *H. pylori*-negative controls. Moreover, silencing of miR-210 in gastric epithelial cells promotes proliferation by activating their target genes, such as Stat3, a well-known protein upregulated in solid tumors, and demethyldenosine transferase DIMT1. Methylation levels of miR-34b/c are higher in gastric mucosa from patients with multiple gastric cancer than in mucosa from patients with single gastric cancer or mucosa from *H. pylori*-positive healthy individuals. In addition, CagA enhanced DNMT3B expression and attenuated miR-26a and miR-101 expression. This suppressed let-7 expression by histone and DNA methylation, leading to Ras upregulation.

**CONCLUDING REMARKS**

*H. pylori*-driven inflammation can stimulate methylation of CpG islands located in a gene encoding tumor suppressors and related proteins. However, the molecular mechanisms underlying aberrant methylation of CpG islands remain largely unknown. Chronic inflammation is accompanied by an influx of neutrophils and macrophages, which generates and release ROS and RNS capable of causing inflammation and DNA damage. A recent study suggests that increased ROS may affect DNA methylation patterns, thereby causing aberrant gene expression. It has been shown that prolonged exposure to H2O2 induces significant hypermethylation of the E-cadherin promoter in a liver cancer cell line. H2O2 upregulates expression of Snail in human hepatoma cells. Snail represses E-cadherin expression by binding to E-box in the E-cadherin promoter and thereby induces DNA methylation of the E-cadherin promoter. Snail

![Figure 2. Generation of ROS/RNS driven by *Helicobacter pylori* infection regulates the redox-sensitive signal molecules which leads to enhancement of snail and DNMTs expression. Snail recruits DNMTs and induces aberrant methylation of CpG islands located in the promoter region of genes encoding cellular signal molecules such as E-cadherin or p14ARF, etc. ROS, reactive oxygen species; RNS, reactive nitrogen species; DNMTs, DNA methyltransferases.](image-url)
induced DNA methylation of the E-cadherin promoter by recruiting histone deacetylase and DNMT1. These findings suggest that oxidative stress functions as a major cause in methylation of the genes. H. pylori has been known to increase the expression of DNMTs. High expression of DNMT3 is associated with metastasis of gastric cancer. DNMT3a rs1550117 polymorphism is significantly associated with an increased risk of H. pylori infection. The level of Snail protein is increased in H. pylori-infected epithelium in clinical samples. Expression of DNMT has been known to be regulated by ROS through activation of c-Jun-N-terminal kinase. Taken together these findings, it is likely that ROS/RNS induced by H. pylori infection can enhance the expression of Snail and recruit the DNMT1 and histone deacetylase, thereby inducing aberrant promoter methylation of genes encoding cellular signaling molecules related to carcinogenesis (Fig. 2). In addition, ROS/RNS produced by H. pylori-induced inflammation may regulate the expression of DNMTs, thereby stimulating methylation of target genes involved in gastric carcinogenesis.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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