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REVIEW

Helicobacter pylori eradication to prevent gastric cancer: Underlying molecular and cellular mechanisms

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Abstract

Numerous cellular and molecular events have been described in development of gastric cancer. In this article, we overviewed roles of *Helicobacter pylori (H pylori)* infection on some of the important events in gastric carcinogenesis and discussed whether these cellular and molecular events are reversible after cure of the infection. There are several bacterial components affecting gastric epithelial kinetics and promotion of gastric carcinogenesis. The bacterium also increases risks of genetic instability and mutations due to NO and other reactive oxygen species. Epigenetic silencing of tumor suppressor genes such as RUNX3 may alter the frequency of phenotype change of gastric glands to those with intestinal metaplasia. Host factors such as increased expression of growth factors, cytokines and COX-2 have been also reported in non-cancerous tissue in *H pylori*-positive subjects. It is noteworthy that most of the above phenomena are reversed after the cure of the infection. However, some of them including overexpression of COX-2 continue to exist and may increase risks for carcinogenesis in metaplastic or dysplastic mucosa even after successful *H pylori* eradication. Thus, *H pylori* eradication may not completely abolish the risk for gastric carcinogenesis. Efficiency of the cure of the infection in suppressing gastric cancer depends on the timing and the target population, and warrant further investigation.

Key words: Helicobacter; Cancer; Gastric acid; p53; Inflammation; Gastric atrophy; Intestinal metaplasia

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INTRODUCTION

Gastric cancer is one of the most common neoplasmas worldwide, accounting for over 870 000 new cases and over 650 000 deaths annually[1]. Mortality from gastric cancer is the second most in death from malignancies, following to lung cancer. With exceptions in countries that have developed screening programs for early diagnoses, most patients reach treatment with cancers already in advanced stages[2]. Since surgery can be palliative, and gastric cancers are largely resistant to chemotherapy and radiotherapy, advanced gastric cancer has a poor prognosis. Therefore gastric cancer still remains a major clinical challenge and a great public health concern.

Extensive epidemiologic studies have shown that *Helicobacter pylori (H pylori)* infection is a major risk factor for developing gastric cancer and its precursor lesions[3]. The bacterium affects more than 50% of the world popultion[4]. The risk of patients with *H pylori* infection developing gastric cancer is in the order of two- to six-fold according to most retrospective case-control and prospective epidemiologic studies[5]. Furthermore, some of the trials eradicating *H pylori* have shown that cure of the infection reduces development of gastric cancer in high risk populations[6-8]. Thus, a hope is emerging and growing that cure of the *H pylori* infection may reduce incidence of gastric cancer.

The goal of this review is to clarify whether eradication *H pylori* results in eradication of gastric cancer. To accomplish this, we will discuss what types of cellular and molecular events occur in the *H pylori*-infected gastric mucosa; what bacterial factors are involved in the process of gastric carcinogenesis; and what host factors are able or unable to be reversed after the cure of the infection.

CELLULAR BASIS OF *H PYLORI*-RELATED GASTRIC CARCINOGENESIS

Histopathologic alterations

Chronic infection with *H pylori* causes active inflammation of gastric mucosa in majority of the population, although it is mostly asymptomatic. The bacterium also alters physiologic and histological behaviors of gastric mucosa, including hypochlorhydria, hyperchlorhydria, and changes in mucosal population of gastric epithelial cells that are specifically differentiated. In the hypochlorhydric population, hypergastrinemia occurs, while parietal cells do not respond to gastrin to produce acid, probably due to corpus inflammation. Apoptotic loss of superficial epithelial cells in the process of differentiation and migration in gastric glands increases[9], while proliferation of neck cells also increases possibly by some sort of compensation and by transactivation of growth stimuli in gastric mucosa[10]. In corpus mucosa, parietal cell population is also diminished in a long term, which is associated with alteration in population of other types of cells in each gland. Together with lowered density of glands partly due to inflammatory and edematous changes in subepithelial tissues, the above changes are known as gastric mucosal atrophy or atrophic gastritis. In addition, epithelial clones with incomplete and complete intestinal phenotypes emerge in the long-term process.

Currently, origins of the epithelial clones for the intestinal metaplasia have not yet been clearly determined. It is likely that epithelial clones for incomplete and complete intestinal metaplasia are developed from gastric epithelial cells by an activation of a series of genes including cdx-1/cdx-2[11-16]. In addition, bone marrow-derived adult somatic stem cells are involved in the regeneration of gastric glands, and may be another source of epithelial population[17]. Although our own study suggest that bone marrow-derived epithelial cells do not harbor permanently in a gastric gland, gastric adenocarcinomas are recently reported to be bone marrow-derived[18]. Stem cells in gastric glands locate neck region, whereas those in intestinal glands reside bottom region, a location completely different from the neck. Transdifferentiation of gastric gland cells to metaplastic cells remains an important question in gastric carcinogenesis.

Bacterial and/or host factors affecting the histologic alterations

Several pathogenic factors of *H pylori* have been demonstrated to be involved in the above alterations in gastric mucosa and the following development of gastric diseases.

Ammonia (NH_3), produced by *H pylori* urease, has been shown to cause acute gastric injury[19] in rats *in vivo* and to accelerate gastric epithelial cell death *in vitro*[19-21]. Chronic administration of NH_3, whose concentration is comparable to that found in *H pylori*-infected patients, increases epithelial cell replication and epithelial cell turnover, associated with accelerated epithelial cell death, cell exfoliation, preferential loss of parietal cells and gastric mucosal atrophy[22, 23]. The damaging effects of NH_3 on gastric mucosa are pH-dependent, while sodium hydroxide at the same pH does not cause significant mucosal injury[19]. Ammonia dissolves readily in water where it forms, and is in equilibrium with, ammonium ions (NH_4^+). With decreases in pH, NH_4^+ predominates, but increases in pH may materially increase levels of non-ionized NH_3[19]. On the other hand, *per os* administration with ammonium chloride (NH_4Cl) results in intragastric NH_4^+, and does not induce significant mucosal atrophy. Rather, NH_4Cl is reported to stimulate antral mucosa to increase gastrin release[24], which possibly induces gastric mucosal hypertrophy[25]. Therefore, not only *H pylori* but also gastric acid secretion of the host is an important determinant of gastric cell kinetics.

NH_3 also increases incidence and size of gastric adenocarcinomas in rats pretreated with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)[26, 27]. Prior administration of NH_3 followed by MNNG does not increase incidence of gastric adenocarcinomas in rats, indicating that NH_3 may act as a promoter in the chemically-induced gastric carcinogenesis. Immunohistochemical analysis using bromo deoxy-uridine (BrdU) demonstrates that NH_3 increases cell replication in gastric tumors as well as non-cancerous tissues surrounding the tumors. Thus, NH_3 and the consequent host epithelial responses play important roles not only in increased cell proliferation in untransformed gastric mucosa but also in promotion of gastric cancer.

The other virulence factors including CagA and other cag pathogenicity island (PAI) proteins, VacA and adhesions have been considered to be involved in wide diversity of *H pylori*-related diseases. For an example, strains containing the cag PAI have been reported to trigger signaling cascades in gastric epithelial cells, resulting in NF-κB activation and other cellular responses. Furthermore, CagA, which can be injected into the host cells, is able to be phosphorylated in the host, and to alter epithelial morphology probably through signaling pathway similar to that of HGF/c-met[28-31]. Roles of phosphorylated CagA protein in gastric epithelium are under extensive investigation and reviewed elsewhere[32]. Since it is related to gastric inflammation, cag PAI may stimulate indirectly excessive production of reactive oxygen species, including nitric oxide, and lead to programmed cell death. Indeed, studies show conflicting results for an association between cag PAI and apoptosis[33, 34].

VacA reportedly induces gastric epithelial cell apoptosis[35, 36]. It is found that VacA also induces apoptosis of marophages and suppresses T-cell responses[37-40]. Shibayama *et al*[41] showed that γ-glutamyl transpeptidase induces apoptosis. Furthermore, several apoptotic mediators such as TNF-α, FAS-ligand, TRAILs and their receptors are reported to be upregulated[42-44]. Thus, proapoptotic factors from either the bacterium or the host appear to be involved in altered cell kinetics as well as disturbed immunologic surveillance in gastric mucosa. Once certain clones acquire the resistance from apoptotic or immunologic surveillance, they begin to grow to form clusters of neoplastic phenotypes.

MOLECULAR ALTERATIONS OF *H PYLORI*-RELATED GASTRIC CARCINOGENESIS

Events promoting gastric carcinogenesis

Gastric cancer is divided into two histologic entities: 'in-

testinal-type' and 'diffuse-type'. These two types differ in epidemiology and clinical outcome. Molecular profiles are also distinct between these phenotypes[45-47], and actually consist of wide variety of alterations including mutations, loss of heterozygosity (LOH), and epigenetic changes of expression of unmutated genes(Table 1). It is not surprising that numerous reviews have been published regarding this topic[45-52], considering the size of population with gastric cancers or with *H pylori* infection. In diffuse-type gastric adenocarcinomas, DNA-repair errors, p16 suppression and cyclin E amplification occur frequently in early stages. In early stages of intestinal-type gastric adenocarcinomas, inactivation of APC due to LOH or mutation and nonfunctioning p53 frequently occur. Events due to changes in tumor microenvironments, *i.e.,* overexpression or transactivation of growth factors such as EGF-family growth factors (TGFα, EGF, HB-EGF, etc), insulin-like growth factors (IGF-1 and IGF-2), transforming growth factor-β, cytokines, and gastrin, also play important roles in phenotypic change in gastric epithelial cells [53, 54]. For an example, elevated gastrin may transactivate HB-EGF and its receptors, resulting in upregulation of mitogen-inducible cyclooxygenase (COX-2) and its products (prostaglandin E_2, etc)[55, 56].

Recently, COX-2[57-71] attracts attention of many oncologists and gastroenterologists. In fact, some epidemiologic studies have shown that a long-term NSAID-use results in significant reduction of incidence and mortality of digestive cancers including not only colon but also stomach[72, 73]. We have shown that the COX-2 overexpression alters cell kinetics, suppresses programmed cell death, induces invasive phenotypes, supports tumor angiogenesis and influences cell adhesion to endothelial cells[54, 70, 71, 74-79]. *H pylori* infection induces gastric COX-2 upregulation[71, 80-86], and cure of the infection reduces the COX-2 expression[70]. However, in mucosa with intestinal metaplasia, COX-2 is overexpressed even after the cure of the infection (Figure 1)[70]. Procarcinogenic effects of COX-2 on stomach could be only partially reversed by successful *H pylori* eradication. Similar findings were also observed in the case of expression of nitrotyrosine, a product of nitric oxide (NO), in precancerous gastric mucosa. Expression of nitrotyrosine is elevated in gastric mucosa in patients with *H pylori* gastritis, which is reversible after successful *H pylori* eradication. However, in gastric mucosa with intestinal metaplasia, nitrotyrosine continue to be overexpressed even after the cure of the *H pylori* infection, suggesting that NO and other reactive nitrogen species is highly produced in metaplastic lesions[70].

Mismatch repair deficiency

Microsatellite instability (MSI) is defined as the presence of replication errors in simple repetitive microsatellite sequences due to mismatch repair (MMR) deficiency[48]. It is classified as high-frequency (MSI-H), low-frequency (MSI-L) or stable (MSS)[87]. MSI has been recognized as one of the earliest changes in carcinogenesis and results in genomic instability. MSI is detected not only in gastric cancer but also in intestinal metaplasia from subjects both with and without gastric cancer[88], suggesting that MSI can be an early event in gastric carcinogenesis[89-91]. Further-

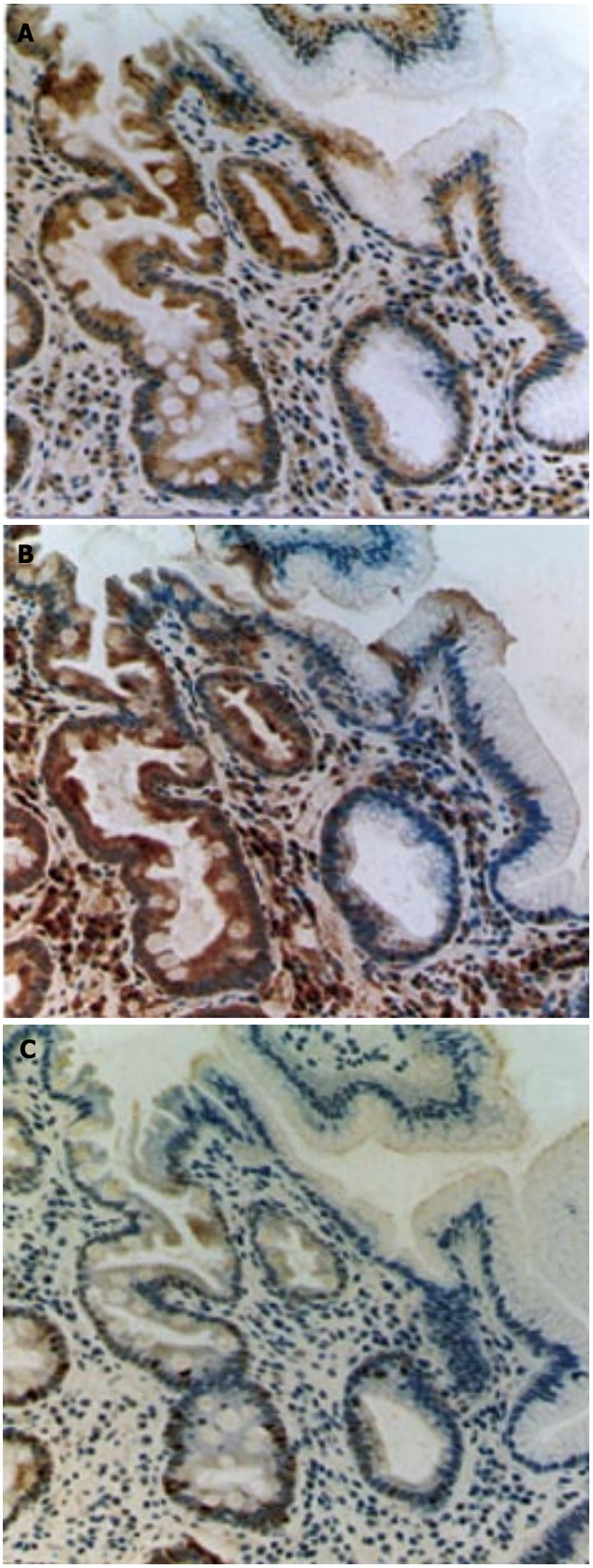

Figure 1 Expression of COX-2, nitrotyrosine and Ki-67 immunoreactivity in human gastric mucosa with intestinal metaplasia after cure of the H pylori infection. **A**: COX-2 immunostaining; **B**: nitrotyrosine immunostaining; **C**: Ki-67 immunostaining. The overexpression of COX-2 and nitrotyrosine, adduct of nitric oxide, are reported in gastric mucosa with *H pylori* infection[66, 68, 70, 71]. In these photographs, metaplastic gland with goblet cells (in the left side of each photograph) and non-metaplastic gastric glands (in the right side) are shown. COX-2 and nitrotyrosine immunoreactivities continue to exist in gastric mucosa with intestinal metaplasia after the successful *H pylori* eradication with PPI-triple therapy.

Table 1 Molecular alteration in the process of gastric carcinogenesis

Molecules	Major alterations	Comments	Category
p53	Mutation, LOH	Reported in diffuse-type and intestinal-type adenocarcinomas, as well as some precancerous lesions.	Tumor suppressor
APC	Mutation, LOH	Reported in diffuse-type and intestinal-type adenocarcinomas, as well as some precancerous lesions.	Tumor suppressor
DCC	LOH	Reported in intestinal-type adenocarcinomas. Related to cell adhesion	Tumor suppressor
CDH1	Mutation	Reported in diffuse-type adenocarcinomas.	Tumor suppressor
β-catenin	Mutation	Reported in intestinal-type adenocarcinomas.	Tumor suppressor
Fhit	LOH or deletion at chr. 3p14.2	Reported in diffuse-type and, in less frequency, intestinal-type adenocarcinomas, as well as some precancerous lesions.	Tumor suppressor
RUNX3	Hypermethylation	Related to TGF-β/SMAD signaling.	Tumor suppressor
K-ras	Mutation	Reported in intestinal-type adenocarcinomas. An element in signal transduction regulating cell proliferation, etc..	Oncogene
bcl-2	LOH	Reported in intestinal-type adenocarcinomas. Anti-apoptotic factor.	Oncogene
c-met	Amplification	Reported in diffuse-type and intestinal-type adenocarcinomas. The HGF receptor / tyrosine-kinase. Upregulation without mutation is also reported after mucosal injury.	Oncogene / Growth stimulus
c-erbB2	Amplification	Reported in intestinal-type adenocarcinomas. One of receptor-tyrosine kinases for EGF-family proteins.	Oncogene / Growth stimulus
Cyclin E	Amplification	Reported in diffuse-type and intestinal type adenocarciomas.	Cell cycle regulator
K-sam	Amplification	Reported in diffuse-type adenocarcinomas. One of bFGF receptor family proteins, FGFR2.	Oncogene
Mismatch repair (MMR) genes	Silencing due to hypermethylation	Reported in diffuse-type and intestinal-type adenocarcinomas, as well as some precancerous lesions. A possible source of mutations of other genes involving gastric carcinogenesis.	Determinants of microsatelite instability (MSI)
MMR genes	Mutation	Reported in diffuse-type and intestinal-type adenocarcinomas. There are conflicting data suggesting that mucosa with intestinal metaplasia is prone to and resistant to MSI.	Determinants of MSI
EGFR	Overexpression	Reported in diffuse-type and intestinal-type adenocarcinomas.	Growth stimulus
EGF	Overexpression	Reported in diffuse-type and intestinal-type adenocarcinomas.	Growth stimulus
TGF-α	Overexpression	Reported in diffuse-type and intestinal-type adenocarcinomas, as well as some precancerous lesions. Another EGF-family protein.	Growth stimulus
VEGF	Overexpression	Reported in diffuse-type and intestinal-type adenocarcinomas.	Angiogenic factor
iNOS	Overexpression	Reported in diffuse-type and intestinal-type adenocarcinomas, as well as some precancerous lesions and mucosa with H. pylori.	Enzyme
COX-2	Overexpression	Reported in diffuse-type and intestinal-type adenocarcinomas, as well as some precancerous lesions and mucosa with H. pylori. Cytokines and growth factors are possible inducer of COX-2.	Enzyme
ODC	Overexpression	Reported earlier in gastritis.	Enzyme
Telomerase	Activated	Enlongs telomere and prevents cell senescence.	Enzyme
CDXs	Overexpression	Reported in diffuse-type and intestinal-type adenocarcinomas, as well as precancerous lesions. Is involved in intestinal metaplasia.	Transcription factor
Ets1	Overexpression	A transcription factor involving angiogenesis.	Transcription factor
NF-κB	Overexpression	A transcription factor regulating expression of proinflammatory cytokines, chemokines, iNOS and COX-2.	Transcription factor
Sp-1	Overexpression	Reported in diffuse-type and intestinal-type adenocarcinomas.	Transcription factor
SC-1	Overexpression	Reported in diffuse-type adenocarcinomas.	Apoptosis receptor
Fas/CD95	Overexpression	Reported in diffuse-type adenocarcinomas.	Apoptosis receptor
E-cadherin	Mutation	Reported in diffuse-type and intestinal-type adenocarcinomas.	Cell adhesion
CD44	Splicing variant	Reported in diffuse-type and intestinal-type adenocarcinomas.	Cell adhesion
Gastrin	Elevation in serum	Elevation of amidated gastrin is reported. Transactivates EGF-family proteins.	Gut hormone

more, hypermethylation of CpG islands in the promoter region of the hMLH1 gene is associated with decreased hMLH1 protein, and often occurs in gastric cancer cases with MSI-H, indicating that epigenetic inactivation of hMLH1 may underlie MSI[92]. MSI in gastric cancer is associated with antral tumors, intestinal-type differentiation, and a better prognosis. Cancer cases with MSI exhibit mutations in BAX, hMSH3, hMSH6, E2F-4, TGF-β receptor II, and IGF-R II, which have simple tandem repeat sequences within their coding regions[93-99]. *H pylori* infection and following gastric mucosal alteration are closely related to MSI[100-102]. In particular, Park *et al*[100] recently reported an immunohistochemical study demonstrating that DNA MMR protein expression (hMLH1 and hMSH2) decreases in patients with *H pylori* infection. Cure of the infection resulted in significant increases in the percentage of hMLH1 (76.60 ± 20.27, 84.82 ± 12.73, $P = 0.01$) and hMSH2 (82.36 ± 12.86, 88.11 ± 9.27, $P < 0.05$) positive epithelial cells[100], suggesting that the effects of *H pylori* on MSI are reversible at least in a part. On the other hand, MSI results in frame-shift mutations of hMSH3 and hMSH6, and loss of hMSH1 and hMSH2 functions, which may lead gastric

Table 2 "p53" mutation in gastric cancers of early stages and precancerous gastric lesions. In gastric cancers of early stages and precancer gastric lesions, LOH and splicing are merely reported. Abbreviations for mutation: Del: deletion; Ins: insertion; F/S: frame shift. Abbreviati for lesion: EGC: early gastric cancer; AD: adenoma, CA/AD: carcinoma in adenoma; D: dysplasia; IM: intestinal metaplasia; N: muc without dysplasia, IM or carcinoma. Data are collected from references 104, 105, 113-118. (Modified from Tsuji *et al*[119, 120])

First author	Year	Case	G:C→A:T	G:C→T:A	A:T→G:C	A:T→C:G	A:T→T:A	G or C	Del	Ins	F/S	Lesions
Yokozaki	1992	1			2	1	1	1				EGC
Tohdo	1993	5			3						1	AD or CA/AD
Uchino	1993	12	10			2		1				EGC
Correa	1994	8	4		3				1			D, IM, or N
Hongyo	1995	9	10					1	1	2		Cancer at stage I
Sakurai	1995	7	4									AD, CA/AD or EGC
Tamura	1995	1	1									AD
Tamura	1995	4	3	2								EGC
Ranzani	1995	18	13	1			1	1	1	2		EGC
Summary			45	3	8	3	2	3	4	4	1	
(%)			62	4	11	4	3	4	5	5	1	

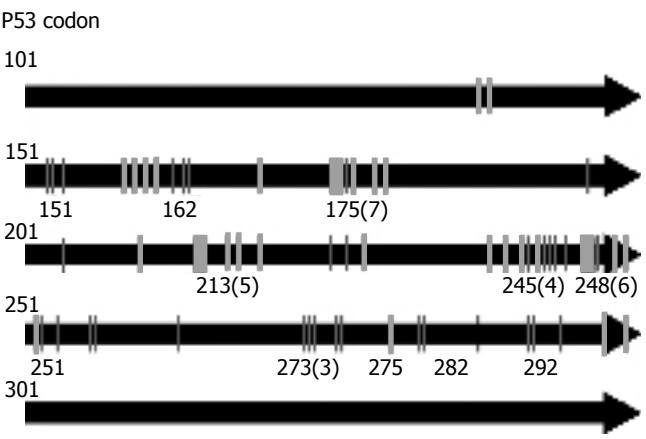

Figure 2 Location of point mutations of p53 in gastric cancers and premalignant lesions of the stomach. Horizontal lines mean codons of p53 gene. Thick and thin vertical lines respectively mean 5 and 1 mutations of the corresponding codon. Gray numbers indicate location of mutated codon followed by number of mutated cases in parentheses. As shown in this figure, codons 175, 213, 245, and 248 are preferably mutated in early stages of gastric cancer. Data are collected from references 104, 105, 113-118.

epithelial cells to further genetic instability that cannot be reverted by *H pylori* eradication. Therefore, the precise mechanism for *H pylori*-induced suppression on MMR protein has not yet been clarified and one of the important topics in *H pylori*-related gastric carcinogenesis.

Oncogenes

Certain EGF-like growth factors and their receptors are activated by membrane-type proteases called ADAMs (a disintegrin and metalloproteinase) following the stimulation including gastrin[56], endothelin and IL-8 that have G-protein coupled receptors[103]. IL-1β is also known to transactivate EGF-receptor via pathways dependent and independent of IL-8[103].

In addition, certain growth factors, their receptors and components of intracellular signaling have mutations or amplifications activating cell growth, inhibiting programmed cell death, and altering cell phenotypes. These oncogenes include HGF receptor (c-met), c-erbB2 (HER-2/neu), c-erbB3, K-sam, ras, c-myc and others, and have been reported to be mutated, amplified, or overexpressed in the process of gastric carcinogenesis[47, 52]. Once these oncogenes are mutated, it would be hardly possible for *H pylori* eradication to suppress oncogenes.

Tumor suppressor genes

Various tumor suppressor genes have been reported to be inactivated and involved in gastric carcinogenesis. For example, inactivation of p53 and p16 has been shown in both diffuse- and intestinal-type gastric cancers[52,104,105]. On the other hand, mutation of adenomatous polyposis coli (APC) gene occurs more often in intestinal-type gastric cancer. Another important tumor suppressor gene in intestinal-type gastric cancer is runt-related gene 3 (RUNX3) coding a subunit of polyomavirus enhancer binding protein 2[106-110], since expression of RUNX3 is greatly reduced in intestinal metaplasias in human stomachs[111] and Runx3-/- mouse gastric epithelial cells have a potential to differentiate into Cdx-2 positive intestinal type cells[112]. The product of the gene appears to interact with smad 2/3, which mediates TGF-β signaling pathway, and induces $p21^{WAF1/Cip1}$ expression.

Inactivation of these tumor suppressor genes includes, inactivating mutations, LOH, and epigenetic silencing. For example, hot spot mutations on CpG islands in p53 have been reported not only in gastric cancers at early stages but also in non-cancerous tissues with intestinal metaplasia [104, 105, 113-118]. In stomach, mutated p53 proteins are largely non-functioning and accumulate in the cells. Interestingly, p53 mutation frequently include G:C→A:T transition (Table 2, Figure 1)[119, 120], and NO is an important mutagen causing this type of mutation[120-122]. On the other hand, silencing of RUNX3 by promoter hypermethylation is frequently found in gastric cancers and in intestinal metaplasia. Although the silencing of tumor suppressor genes due to mutation may not be reversed, the epigenetic silencing may be reversed in methylation and demethylation processes. At present, there is no evidence indicating *H pylori per se* increases aberrant hypermethylation of tumor suppressor genes[123]: rather, Epstein-Barr virus-related gastric cancer is associated with a high frequency of DNA

hypermethylation, suggesting that viral oncogenesis might involve DNA hypermethylation with inactivation of tumor suppressor genes[124]. However, male gender, intestinal metaplasia and chronic inflammation with monocytic infiltration are strongly associated with increased methylation in non-cancerous gastric mucosa[123], and *H pylori* infection is one of the major causes of gastric inflammation. Thus, it remains an important question whether cure of the infection reduces the epigenetic alterations in tumor suppressor genes in non-transformed gastric epithelia.

Telomere and/or telomerase

Activation of telomerase that prevents shortening of telomeres during cell division may play an important role in immortalizing cells[47, 125-127]. In brief, telomeres cover the ends of chromosomes and are important in maintaining chromosomal integrity. In intestinal metaplasia, shortening of telomeres[52] as well as telomerase activation[127, 128] are observed, suggesting an important role in development of gastric cancer with intestinal type. Interestingly, it has been reported that *H pylori* infection reactivates telomerase[129, 130], and that cure of the infection appears to reduce telomerase activity[130]. Since clinical studies using human subjects may suffer from sampling errors, it remains an open question whether *H pylori* eradication reverses telomerase activation.

HOST GENETICS OF *H PYLORI*-RELATED GASTRIC CARCINOGENESIS

Genetic predisposition affecting inflammation and acidity of stomach

Genetic predisposition plays an important role in developing gastric cancer. The most widely reported are IL1B and NAT1 polymorphisms[131-138]. The association of IL1B polymorphism and gastric carcinogenesis was hypothetically explained by El-Omar *et al*[134] to be a strong acid-inhibiting and proinflammatory capacity of the gene product. Indeed, gastric acid secretion is known to be suppressed by IL-1β, which is mediated by nitric oxide[139]. These genetic factors may have strong association with *H pylori* infection, since the bacterium induces production of interleukins, inflammation, and elevates intragastric pH, which may result in increase of xenobiotic products. On the other hand, IL-1β and IL-8 were recently reported to transactivate EGF-receptor *via* ADAM-10 activation[103]. IL-1β is also known to up-regulate COX-2 in gastric epithelium[140]. Therefore, the reason for the association of IL1B polymorphisms and the risk for gastric cancer remains an open question and may require further investigation.

Genetic predisposition possibly independent of acidity of stomach

Another example of the genetic predisposition is families of hereditary nonpolyposis colorectal cancer (HNPCC) kindred of which have an excess of gastric carcinoma; complete intestinal metaplasia and chronic atrophic gastritis restricted to the antrum[141-143]. Interestingly, HNPCC patients frequently have a mutation in one of two DNA mismatch repair genes, hMSH2 or hMLH1, and demonstrate MSI-H. As mentioned earlier, *H pylori* has an ability to decrease MMR activity. Several genetic predispositions in MSI may share the same mutations to those found in *H pylori*-induced carcinogenesis. In these cases, the bacterial infection has a potent impact on gastric carcinogenesis, since it could lower the MMR activity more than the hereditary predisposition alone.

Hereditary gastric cancer due to germline mutation of the E-cadherin has been reported[144], which is a risk factor possibly independent of *H pylori* infection.

DOES *H PYLORI* ERADICATION ERADICATE GASTRIC CANCER?

Unlike the typical adenoma-carcinoma sequence of colon, development of gastric cancer appears to be a complex process. Due to the complexity of molecular events of gastric carcinogenesis, factors discussed here do not cover every aspect of gastric carcinogenesis. Rather, we tried to overview some of the possible factors initiating, promoting and supporting the development of gastric cancer. By doing so, we discussed what types of risks exists in *H pylori* positive subjects and what extent of these risks could be withdrawn after the cure of the infection.

Certain bacterial factors affect gastric epithelial cells directly to support establishment and development of metaplastic or dysplastic clones. Successful *H pylori* eradication withdraws these bacterial factors and therefore lowers the promotional effects on tumor development. The bacterium also increases genetic instability and risks of mutation. Some host factors such as NO and other reactive oxygen species are induced by *H pylori* and increase risks of mutation. Although cure of the infection may reduce these risks leading to epithelial mutagenesis, it does not abolish the risk completely. Particularly, in gastric mucosa with intestinal metaplasia and other phenotypically altered tissues, increases in MSI and NO synthesis, as well as COX-2 overexpression are unaltered after the cure of the *H pylori* infection. Thus, *H pylori* eradication is an effective strategy in reducing the risk of gastric cancer; however, it is not efficient enough to eradicate gastric cancer. Prevention of the infection, *H pylori* immunization, *H pylori* eradication in the youth, selection of the high risk population, and alternative chemopreventive measures may be essential for optimal management of malignancy of the stomach.

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