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Helicobacter pylori as an oncogenic pathogen, revisited

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Abstract

Gastric cancer is an inflammation-associated malignancy aetiologically related to infection with the bacterium, *Helicobacter pylori*, which is considered a necessary but insufficient cause. Unless treated, *H. pylori* causes life-long acute and chronic gastric inflammation resulting in progressive gastric mucosal damage that may result in gastric cancer. The rate of progression from superficial gastritis, to an atrophic metaplastic mucosa, and ultimately to cancer relates to the virulence of the infecting *H. pylori* as well as host and environmental factors. *H. pylori* virulence is a reflection of its propensity to cause severe gastric inflammation. Both mucosal inflammation and *H. pylori* can cause host genomic instability, including dysregulation of DNA mismatch repair, stimulation of expression of activation-induced cytidine deaminase, abnormal DNA methylation and dysregulation of micro RNAs, which may result in an accumulation of mutations and loss of normal regulation of cell growth. The difference in cancer risk between the most and least virulent *H. pylori* strain is only approximately 2-fold. Overall, none of the putative virulence factors identified to date have proved to be disease-specific. The presence, severity, extent and duration of inflammation appear to be the most important factors and current evidence suggests that any host, environmental or bacterial factor that reliably enhances the inflammatory response to the *H. pylori* infection increases the risk of gastric cancer.

Introduction

The association between gastric cancer, peptic ulcer and gastric inflammation (gastritis) has been recognised since at least the late 19th century (Ref. 1). Gastric cancer was one of the most common, if not the most common, cancer in most Western countries throughout the first half of the 20th century (Ref. 2). The high prevalence, morbidity and mortality of peptic ulcer disease and gastric cancer resulted in a correspondingly high interest in understanding their pathogenesis as well as the role of the gastritis in their pathogenesis (Ref. 3). The 20th

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century saw a marked decline in the incidence gastric cancer and a parallel increase in duodenal ulcer disease (Refs 2, 4). In the early 1980s, Warren and Marshall proved that *Helicobacter pylori* was a cause of gastritis and suggested that the infection might also be aetiologically responsible for both peptic ulcer disease and gastric cancer (Ref. 5).

In 1994, based largely on epidemiological studies, *H. pylori* was defined as a class I human carcinogen (Ref. 6). Although epidemiologic studies showed that approximately half of the world's population was infected with *H. pylori*, in some areas gastric cancer was rare despite the high prevalence of *H. pylori* infections (Ref. 7). This suggested that *H. pylori* strains might differ in their propensity to cause cancer and these differences might be responsible for the markedly geographic differences in *H. pylori*-related diseases (Ref. 2). It was also discovered that the clinical manifestations of *H. pylori* infection could rapidly change (Refs 8, 9, 10) exemplified by the marked decline in the incidence of gastric cancer and increase in duodenal ulcer experienced during the 20th century in Western countries (Ref. 4).

Research related to *H. pylori* initially focused on attempting to understand the role of the organism in disease pathogenesis. The importance of the host and environment were most often studied separately. Recently, it has become clear that the interactions between the bacterium, the host and enviromnent are critical in dictating outcome (Refs 8, 11).

H. pylori is a necessary agent for gastric cancer

Gastric cancer is an inflammation-associated cancer with *H. pylori* infection being the most common cause of progressive and persistent inflammation that eventually results in gastric cancer (Ref. 8). The infection results in a cascade of histologic changes beginning with mild superficial gastritis and that may eventually result in gastric atrophy during which the normal gastric mucosa is converted into a metaplastic epithelia (Ref. 12). This also results in a progressive reduction in the gastric acid barrier that inhibits other bacteria from populating the stomach (Ref. 3). Cure of *H. pylori* infection halts the progression of mucosal damage, resolution of the resulting acute and chronic inflammation, and healing of any still reversible damage. It is now recognised that worldwide gastric cancer can be largely be eliminated by *H. pylori* eradication (Refs 8, 14, 15). Even among those infected and at risk, the risk of developing gastric cancer is reduced following *H. pylori* eradication. *H. pylori* eradication prevents further the progression of damage and 'locks in' or reduces the level of risk present at the time of eradication, but does not eliminate the risk of subsequent cancer (Ref. 16).

H. pylori in gastric cancer pathogenesis

Interactions between *H. pylori* infection, the host and the environment serve to either potentate or reduce the risks of any particular *H. pylori*-related clinical outcome (Ref. 17) (Fig. 1). For example, host genetic polymorphisms associated with an enhanced inflammatory response, such as IL-1β–511 T, IL-1B-31 C alleles and IL-1RN *2/*2, also enhance the risk of gastric cancer (Ref. 18). This risk and rate of development of atrophic gastritis and gastric cancer can be further amplified by the infection with a more virulent strain of *H. pylori* (e.g. CagA-positive strains), which are also associated with an enhanced inflammatory host response (Ref. 19). The environment, especially the diet, plays an

especially important modifying role in pathogen–host interactions (Ref. 2). This critical effect of diet can be seen in Japan, a high gastric cancer country. In Japan, the vast majority of infections are caused by highly virulent *H. pylori* strains. Between 1965 and 1995, the incidence of gastric cancer in Japan fell approximately 60% in all age groups (Refs 9, 10). This change occurred despite no change in the virulence of the most common circulating *H. pylori* strain or in the genetics of the hosts (Refs 9, 10). The decline was however associated with environmental changes (i.e. in food preservation from salt to refrigeration, in westernising of the diet, and in a reduction in smoking) (Ref. 9).

Role of *H. pylori* virulence factors

Genomic sequence comparison of clinical *H. pylori* isolates has shown that approximately 7% of the proteins are strain-specific (Ref. 20). Proteins not present in all strains, or a genotype variety that associate with clinical disease are termed disease-associated virulence factors. More appropriately, they should be called putative virulence factors (Table 1) (Refs 7, 21) in that the association of clinical outcome (e.g. duodenal ulcer) and a putative factor may also occur by chance. Suggested criteria for a valid and biologically important virulence factor include: (1) the presence of the factor should reliably correlate with a disease or a significant increase in mucosal inflammation; (2) the association should exhibit epidemiologic consistency across populations and regions; (3) the effect of the factor should have biologic plausibility (e.g. be involved in a relevant biologic process such as inflammation); and (4) the propertied biologic activity should be reduced or eliminated by gene deletion and restored by complementation (Ref. 21).

CagA as a risk factor and as an oncoprotein

Most of the currently recognised putative virulence factors are also associated with enhanced mucosal inflammation (Ref. 7). The most extensively studied virulence factors are the *cag* pathogenicity island (*cag* PAI) and the vacuolating cytotoxin, VacA. The *cag* PAI encodes a type IV secretion system (T4SS) (Ref. 22). The CagA protein is a 120 –145-k immunodominant protein, which is injected into the host cell via the T4SS (Ref. 23). In both humans and experimental animals, CagA expression is associated with a marked host inflammatory response and an increased risk development of mucosal ulcerations and atrophy (Ref. 7). The presence of CagA-positive increased the risk for development of gastric cancer (Ref. 24) approximately 2-fold (odds ratio (OR) = 2.01, 95% confidence interval (CI) = 1.21–3.32) (Ref. 25). Gastritis, peptic ulcer and gastric cancer also occur with CagA-negative *H. pylori* infections, albeit at a lower rate (Ref. 26).

Infection with CagA-positive strains is associated with increase in IL-8 production by infected cells (Refs 27, 28, 29). In vitro experiments have also shown that infection of nonpolarised epithelial cells with CagA positive *H. pylori* produces epithelial cell elongation and scattering, referred to as the ‘hummingbird phenotype’ (Ref. 30).

In vivo studies in a number of different experimental animals have confirmed that CagA-positive infections are associated with an increase in gastric mucosal inflammation (Ref. 31). For example, Mongolian gerbils infected with wild-type CagA develop more severe gastric

inflammation than those infected with CagA-negative strains (Ref. 31). Mongolian gerbils infected with CagA-positive *H. pylori* have been reported to develop gastric dysplasia and even gastric cancer (Refs 32, 33). However, it remains controversial whether the lesions described are actually cancers; the majority of laboratories have been unable to confirm development of cancer (Refs 31, 34, 35) despite use of the same strains of *H. pylori* and long periods of observation (Refs 34, 35). In addition, in Mongolian gerbils gastric cancer has been described to develop within 4 weeks of *H. pylori* inoculation (Refs 31, 33). These results suggest that the lesions described are unlikely to be cancers but rather likely represent gastritis cystica profunda or some related lesions (Refs 36, 37, 38). *H. pylori*-related gastric cancer in mice has also been reported to be cured following *H. pylori* eradication (Refs 39, 40, 41). Nonetheless, experiments using a combination of a low dose of a carcinogen, such as *N*-methyl-*N*-nitrosourea or *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine followed by *H. pylori* infection have conclusively produced gastric cancers when neither used alone would (Refs 38, 42, 43). As we discuss later, these experiments may be the most representative of what typically occurs in humans (see gastric cancer and the gastric microbiome other than H. pylori section).

Transgenic mice that express wild-type or phosphorylation-resistant CagA, either in all their cells, or transcendently in the stomach, have been reported to develop gastric epithelial hyperplasia, gastric polyps and adenocarcinoma (Ref. 44). Loss of CagA in these transgenic mice prevented development of cancer. These observations resulted in the notion that when CagA is widely expressed it may act as an oncoprotein (Ref. 45). However, it remains unclear whether studies with transgenic animals or when CagA is transfected into cells in vitro (in contrast to natural injection via the T4SS) are relevant to the pathogenesis of gastric cancer that occurs following human infection (Ref. 46).

Search for a cancer-specific *H. pylori* gene or virulence factor

CagA subtypes

The suggestion that CagA might be an oncoprotein resulted in investigations as to whether there were differences in CagA obtained from regions that differed in terms of gastric cancer incidence. CagA protein has been subtyped based on the presence of Glu–Pro–Ile–Tyr–Ala (EPIYA) motifs (Ref. 7). Variations in the amino acid sequences flanking the EPIYA motif identified four subtypes: EPIYA-A, EPIYA-B, EPIYA-C and EPIYA-D which allowed CagA from separated into Western (i.e. ABC, ABCC, ABCCC) or East-Asian types (ABD) (Ref. 47). East-Asian-type CagA exhibit stronger in vitro binding affinity for the Src homology 2 domain of the Src homology 2-containing protein-tyrosine phosphatase (SHP2) as well as greater ability to induce the hummingbird phenotype compared to Western-type CagA (Ref. 48). Both types are associated with greater mucosal inflammation than are CagA-negative infections (Ref. 47). East-Asian-type CagA *H. pylori* is also associated with greater mucosal inflammation than infection with the Western-type CagA (Refs 49, 50, 51, 52). These finding have led some to postulate that the increased prevalence of gastric cancer in East Asia may be related to the type of CagA circulating (Ref. 7).

Studies attempting to show a specific relation of CagA and gastric cancer have generally failed. For example, at the beginning of the 20th century, the highest rates of gastric cancer

were present in Europe and those strains did not express the East-Asian type of CagA (Ref. 2). Another more current example is that the mountainous regions of Central and South America are very high-risk areas for gastric cancer despite the fact that their CagA structure is Western type (Ref. 11). Mongolia, another high gastric cancer incidence area in Asia, also has non-East-Asian-type CagA as the predominant type (Ref. 53).

Among those with Western-type CagA it was noted that those with cancer were more likely to have a higher prevalence of multiple EPIYA-C than those infected with strains with a single repeat (Refs 54, 55, 56, 57, 58) leading some to propose that multiple EPIYA-C repeats enhanced carcinogenicity. There has been considerable experimental work in relation to the presence of multiple repeats influence to the degree and duration of phosphorylation-dependent CagA activity (Refs 59, 60). The putative cancer EPIYA-C association is current believed to be spurious as strains with multiple repeats are less able to survive in acid environments (Ref. 56) consistent with multiple repeats arising in response to the development of gastric atrophy rather than being the cause (Ref. 56). That notion is also supported by the observation that in the populations where frequent multiple repeats are present in strains from cancer patients, they were likely acquired as they are rarely present in children in the same population (Ref. 61).

VacA

VacA was originally recognised as a vacuolating cytotoxin based on its ability to cause vacuolation of epithelial cells in vitro (Refs 62, 63). In contrast to CagA, VacA is present in almost all *H. pylori* consistent with it playing an important role in bacterial colonisation or survival. Different *vacA* genotypes are associated with different abilities of the strains to cause cytotoxicity in vitro (Refs 62, 64), although the clinical relevance of cytotoxicity in vitro remains unclear. VacA has been reported to have multiple functions, including a role in the initiation of infection, in modulating lymphocytes, altering membrane permeability and altering autophagy to allow *H. pylori* to survive within mammalian epithelial cells (Refs 65, 66). Although the potential roles of the cytotoxin in disease pathogenesis have been studied extensively in vitro, in vivo correlations are rare and often inconsistent (Refs 67, 68, 69).

Different *vacA* genotypes have been associated with the risk of clinical outcomes such as peptic ulcer or gastric cancer. The gene was divided into two types based on differences in the signal and middle regions (i.e. ‘s’ and ‘m’ types, respectively). The *vacA* s1m1 genotype is associated with the most cytotoxic strains (Refs 62, 63) and with gastric cancer (Ref. 7). A systematic review affirmed the association between *vacA* s1m1 genotypes and peptic ulcer or gastric carcinoma in Latin America, the Middle East, and some Africa countries (Ref. 70). An observational longitudinal study for Spain also reported that *vacA* s1 and m1 strains were more likely to develop preneoplastic gastric lesions (OR = 2.90 and 3.38, respectively) (Ref. 71). In a Portuguese population, s1m1 was associated with increased risk of gastric carcinoma (OR = 17 and 6.7, respectively) (Ref. 19). The *vacA* genotype was subsequently divided into five subtypes [signal (s), intermediate (i), middle (m), deletion (d) and c-type] and almost every imaginable subtype of *vacA* has been evaluated in relation to risk of disease, including i- (Ref. 72), d- (Ref. 73) and c-region genotypes (Ref. 74). The associations with disease frequently differ. For example, i1-type strains were strongly

associated with gastric adenocarcinoma in an Iranian population (Ref. 72), but with peptic ulcer disease and gastric cancer in Western countries (Refs 67, 75, 76, 77).

Despite the interest and the large number of observational studies, the predictive value of *vacA* subtypes has generally failed to achieve the requirements for valid virulence factors. For example, the reports of the predictive value of *vacA* s-, m- and i-region genotypes in Western countries were not confirmed in East and Southeast Asia (Refs 73, 78, 79). The same failure was found for value of differences in the 3′ end region of *vacA*, denoted by c1 and c2 (c1 thought to be more harmful than the c2), which were reported to be strong predictors for gastric cancer in men (Ref. 74). The failure of predictions to achieve consistency across populations most likely reflects different evolution of *vacA* in different populations such that the association is primary with the population with disease associations occurring by chance.

Outer membrane proteins (OMPs)

A number of putative virulence factors enhance the ability of *H. pylori* to interact with the epithelial surfaces especially the bacterial OMPs (Ref. 80). One such virulence factor, the outer inflammatory protein (OipA), has been associated with enhanced inflammation and involved in IL-8 production in the gastric mucosa through interactions with transcription factors nuclear factor-kappaB (NF-κB), AP-1 and ISRE-like element (Ref. 11). The ability of OipA to enhance NF-κB activity is independent of the *cag* PAI (Ref. 81). A multiple logistic regression analysis examined the expression status or presence of the *cag* PAI, VacA, OipA and BabA in various clinical outcomes (Ref. 81) and found that only *oipA* 'on' status was an independent determinant predictor of duodenal ulcer disease (OR = 5.0; 95% CI = 2.1–11.9). A nonoverlapping cohort of 200 patients used immunoblot analysis to study expression of four outer-membrane proteins (OipA, BabA, BabB and SabA) (Ref. 82). Multiple logistic regression showed only OipA-positive status was an independent determinant predictor of gastric cancer (OR = 4.8; 95% CI = 1.4–16.8) and duodenal ulcer (OR = 4.0; 95% CI = 1.6–10.2) (Ref. 82). These results were confirmed by a meta-analysis of 11 studies showing that *oipA* 'on' status showed significant associations with increased risk of peptic ulcer disease (OR = 3.97, 95% CI = 2.89–5.45) and gastric cancer (OR = 2.43, 95% CI = 1.45–4.07) (Ref. 83).

Expression of the blood group antigen-binding adhesin (BabA), which binds to monofucosylated (ABO) and difucosylated (Lewis^b) is thought to be a determinant of the density of *H. pylori* colonisation (Refs 84, 85). In humans, BabA-positive strains have been associated with a 2-fold increase in gastric atrophy compared with infections with BabA-negative strains (Ref. 86). This observation is consistent with studies showing that BabA-positive strains colonise more densely and induce more IL-8 secretion in the mucosa than BabA-negative strains (Ref. 86). As we stress below, it is important to note that OipA, CagA and BabA are typically co-expressed such that the associations found with any putative factor are likely related to the combined action either of different factors or solely to a different factor, or to an as yet unidentified, but linked factor.

Summary of putative virulence factors and disease causation

Associations do not causation make (Ref. 87). The study of associations using individual putative *H. pylori* virulence factors in isolation has generally proved unrewarding. Possibly the most important reason is that the most virulent *H. pylori* organisms co-express many of the putative virulence factors, whereas less virulent strains often fail to produce any (Ref. 7). For example, the Spanish study (Ref. 71) mentioned above that assessed *vacA* status also assessed CagA status and showed that CagA, *vacA* s1m1, positive strains had a 4.80 (95% CI = 1.71–13.5) fold higher disease risk than those infected with CagA-negative, *vacA* s2 m2 strains. The typical virulent strain associated with the presence of marked mucosal inflammation may synergistically interact is CagA-positive, VacA s1, OipA 'on' and BabA positive. Studies using panels of coexpressed virulence factors are generally lacking. It also remains unclear whether such studies will provide important insights other than that obtained by simply identifying enhanced mucosal inflammation as the critical variable. As we have illustrated the numerous studies that failed to take into account the presence of multiple putative virulence factors have rarely provided generalisable insights.

Importantly, none of the putative virulence factors identified to date have proved to be disease-specific. A finding that is consistent with the notion that any host or bacterial factors that reliably enhance the inflammatory response to the infection might be expected to increase the risk of a clinical outcome (Ref. 11).

Bacterial factors associated with genetic instability

As noted previously, the difference in the ability of *H. pylori* strains to elicit mucosal inflammation is likely the best predictor of the risk of a clinically significant outcome, such as gastric cancer (Ref. 7). The degree and rapidity of gastric mucosal damage are also strongly influenced by both the environment (high-salt diet, smoking, mutagens, etc.) as well as the response of the host to inflammation often reflected in polymorphisms of host genes (Ref. 88). All *H. pylori* strains can potentially cause gastric cancer (i.e. no avirulent strains have been discovered to date). The risk is greater (approximately doubled) with more virulent strains (e.g. CagA-positive) (Ref. 46). Genomic instability is a hallmark of cancer. Despite the fact that *H. pylori* induces chronic often life-long inflammation and the production of reactive oxygen and nitrogen species (ROS and NOS) are important, *H. pylori* themselves are not innocent bystanders as *H. pylori* has been shown to be able to induce double-strained DNA breaks both in vitro and in vivo (Ref. 89). The infection is also associated with impaired DNA mismatch repair, aberrant DNA methylation, and abnormal regulation of microRNA regulation (Refs 8, 17, 90) (Fig. 2). Additionally, wherever *H. pylori* are present in the gastric mucosa, it will stimulate activation-induced cytidine deaminase (AID) enzyme (Ref. 91) associated with *H. pylori* induced stimulation of NF-κB that presence in chronic gastritis mucosa with *H. pylori* infection and around half of gastric cancer (Refs 92, 93). The persistent stimulation of AID results an accumulation of nucleotide alterations in the tumour protein p53, a tumour suppressor gene which has been considered as a molecular signature of its involvement in gastric cancer (Ref. 94) resulted by direct or indirect involvement of *H. pylori* virulence factors (Refs 89, 95). It is supported by abundant ROS and NOS (Refs 17, 96). Although *H. pylori*-induced double stranded DNA breaks can be repaired, the prolonged active infection is thought to saturate the cellular

repair mechanisms that then contribute to genetic instability and frequent chromosomal aberrations (Ref. 95). Inadequate resolution of inflammation caused by *H. pylori* infection activates transcription factors and signal transducers-activator of transcription-3 (Ref. 97) to produce epigenetic changes, including alterations in DNA methylation, histone remodelling and the quantity control of messenger RNAs by microRNAs (miRNAs) (Refs 8, 90, 98) (Fig. 2). For example, the level of methylation in gastric mucosa of patients with gastric cancers is up to 30-fold greater than in healthy mucosa (Refs 99) and higher in patients with multiple than single gastric cancers. Histone acetylation enhances transcription (Ref. 100). Additionally, miRNAs, the post-transcriptional gene frequently altered in gastric cancer that influenced onto cell proliferation and inhibition of apoptosis (Refs 101, 102, 103) suggesting a pivotal role in gastric cancer pathogenesis and progression (Ref. 102). Cure of an *H. pylori* infection reduces or eliminates these *H. pylori*-associated molecular abnormalities (Refs 16, 104). Nonetheless, the risk of cancer, while reduced, often does not return to normal (Refs 105, 106). For example, after follow up to 9.5 years of 1131 patients, the risk of developing gastric cancer in the patients cured of *H. pylori* infection (0.23% at 1 year) was significantly lower than those who had persistent infection (0.70%, $P = 0.04$) (Ref. 107). Importantly, the risk of developing gastric cancer is related to the background gastric mucosal atrophy remaining after *H. pylori* eradication therapy (Refs 108, 109, 110). The fact that cancer risk falls significantly even in those with the highest cancer risk (i.e. after endoscopic removal of an early gastric cancer) is consistent with the notion that the organisms themselves play a role in carcinogenesis (Ref. 111).

Gastric cancer and the gastric microbiome other than H. pylori

Gastric cancer is typically associated with reduced acid secretion leading to hypochlorhydria or achlorhydria. Research on gastric atrophy culminated in the mid-20th when it was recognised that atrophic gastritis was the soil for gastric cancer (Refs 3, 112). Duodenal ulcer disease and gastric cancer patients are typically infected with the most virulent strains but those with duodenal ulcer develop gastric cancer only if atrophic gastritis occurs (Ref. 2). The risk for gastric cancer parallels the increase in gastric atrophy and development of a hypo- or anacidic intra-gastric environment. The absence of acid eliminates the antibacterial barrier which promotes the growth of non-*H. pylori* organisms who would have normally been killed by the acid pH (Ref. 13). Decades before the discovery of *H. pylori* it was recognised that this abnormal population of organisms could metabolise dietary constituents such as nitrate and produce carcinogens locally (Refs 113, 114). Of interest, achlorhydria associated with autoimmune gastritis is also associated with an abnormal population of bacteria, local production of carcinogens, but adenocarcinoma of the stomach is rare unless there are also *H. pylori* present (Ref. 115). These natural experiments suggest that the exponential increase in gastric cancer risk associated with increasing *H. pylori*-associated gastric atrophy is actually a recapitulation of the experiments of adding subclinical amounts of a carcinogen to an inflammatory condition to produce a marked increase in the development of cancer (Ref. 116) (Fig. 3). In autoimmune gastritis, the inflammation is primarily lymphocytic and after the gastric corpus is destroyed, inflammation declines. In contrast, in *H. pylori* the inflammation has a very active neutrophilic component and the *H. pylori* themselves play a role in producing genetic instability (Refs 17, 89). *H. pylori* eradication reduces or eliminates the inflammation-associated inhibition of acid production

and also may allow some parietal cells to recover and return some acid secretion to the otherwise achlorhydric stomach, which would then change the microbiota and possibly reduce the production of both inflammation and carcinogens (Refs 8, 117).

Research in progress and outstanding research questions

It remains unclear whether the primary role of *H. pylori* in gastroduodenal diseases is as the source of an acute on chronic infection with chance, diet, host genetics playing the most important roles in defining the eventual outcome (Refs 17, 118) (Fig. 4). Studies searching for disease associations with putative *H. pylori* virulence factor in isolation of other known factors have been especially unrewarding as have most of the available animal models. Data that *H. pylori* itself is an oncogenic bacteria are circumstantial at best as the outcomes of the infection (i.e. duodenal ulcer with high acid secretion and very low risk of cancer, and atrophic gastritis with achlorhydria and high cancer risk both result from infection with strains with the same putative virulence factors). The data seem to support the hypothesis that overgrowth of other non-*H. pylori* organisms in the achlorhydric stomach may be the actual source of carcinogens that interact with the damaged inflamed mucosa to cause cancer. Whole-genome sequencing analysis of *H. pylori* has provided comprehensive information about the 1600 genes content of the different strains sequenced. It is possible that many new genes associated with carcinogenesis and chronic inflammation may yet be found. Following endoscopic removal of an early gastric cancer, patients remain at high risk for a metachronous cancer despite *H. pylori* eradication. This group provides an ideal human laboratory to identify factors promoting and retarding gastric carcinogenesis.

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Conflict-of-Interest

Dr Graham is a paid consultant and has received research funding from RedHill Biopharma regarding novel *H. pylori* therapies and is a consultant to BioGaia regarding the use of probiotics for *H. pylori* infections. Professor Yamaoka and Dr Miftahussurur have nothing to declare.

References

1. Faber K (1935) Gastritis and its consequences. Paris: Oxford University Press
2. Graham DY (2014) History of *Helicobacter pylori*, duodenal ulcer, gastric ulcer and gastric cancer. World Journal of Gastroenterology 20, 5191–5204 [PubMed: 24833849]
3. Graham DY and Asaka M (2010) Eradication of gastric cancer and more efficient gastric cancer surveillance in Japan: two peas in a pod. Journal of Gastroenterology 45, 1–8 [PubMed: 19714291]
4. Baron JH and Sonnenberg A (2002) Hospital admissions for peptic ulcer and indigestion in London and New York in the 19th and early 20th centuries. Gut 50, 568–570 [PubMed: 11889081]
5. Marshall BJ and Warren JR (1984) Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1, 1311–1315 [PubMed: 6145023]

6. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, Schistosomes, Liver Flukes and *Helicobacter pylori* (1994) Infection with *Helicobacter pylori* IARC monographs on the evaluation of carcinogenic risks to humans. Vol 61 Lyon, France: International Agency for Research on Cancer, 177–240 [PubMed: 7715070]
7. Yamaoka Y (2010) Mechanisms of disease: *Helicobacter pylori* virulence factors. Nature Reviews Gastroenterology & Hepatology 7, 629–641 [PubMed: 20938460]
8. Graham DY (2015) *Helicobacter pylori* update: gastric cancer, reliable therapy, and possible benefits. Gastroenterology 148, 719–731 e713 [PubMed: 25655557]
9. Kamada T et al. (2015) Time trends in *Helicobacter pylori* infection and atrophic gastritis over 40 years in Japan. Helicobacter 20, 192–198 [PubMed: 25581708]
10. Wang C, Weber A and Graham DY (2015) Age, period, and cohort effects on gastric cancer mortality. Digestive Diseases and Sciences 60, 514–523 [PubMed: 25274157]
11. Yamaoka Y and Graham DY (2014) *Helicobacter pylori* virulence and cancer pathogenesis. Future Oncology 10, 1487–1500 [PubMed: 25052757]
12. Correa P (1984) Chronic gastritis as a cancer precursor. Scandinavian Journal of Gastroenterology. Supplement. 104, 131–136 [PubMed: 6597545]
13. Ruddell WS et al. (1976) Gastric-juice nitrite. A risk factor for cancer in the hypochlorhydric stomach? Lancet 2, 1037–1039 [PubMed: 62896]
14. Lee YC et al. (2016) Association between *Helicobacter pylori* eradication and gastric cancer incidence: a systematic review and meta-analysis. Gastroenterology 150, 1113–1124 e1115 [PubMed: 26836587]
15. Lee YC et al. (2016) Mass eradication of *Helicobacter pylori* to prevent gastric cancer: theoretical and practical considerations. Gut and Liver 10, 12–26 [PubMed: 26696028]
16. Graham DY and Shiotani A (2005) The time to eradicate gastric cancer is now. Gut 54, 735–738 [PubMed: 15888771]
17. Hanada K and Graham DY (2014) *Helicobacter pylori* and the molecular pathogenesis of intestinal-type gastric carcinoma. Expert Review of Anticancer Therapy 14, 947–954 [PubMed: 24802804]
18. Xue H et al. (2010) Interleukin-1B and interleukin-1 RN polymorphisms and gastric carcinoma risk: a meta-analysis. Journal of Gastroenterology and Hepatology 25, 1604–1617 [PubMed: 20880168]
19. Figueiredo C et al. (2002) *Helicobacter pylori* and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. Journal of the National Cancer Institute 94, 1680–1687 [PubMed: 12441323]
20. Sgouros SN and Bergele C (2006) Clinical outcome of patients with *Helicobacter pylori* infection: the bug, the host, or the environment? Postgraduate Medical Journal 82, 338–342 [PubMed: 16679473]
21. Lu H, Yamaoka Y and Graham DY (2005) *Helicobacter pylori* virulence factors: facts and fantasies. Current Opinion in Gastroenterology 21, 653–659 [PubMed: 16220040]
22. Censini S et al. (1996) cag, a pathogenicity island of *Helicobacter pylori,* encodes type I-specific and disease-associated virulence factors. Proceedings of the National Academy of Sciences of the United States of America 93, 14648–14653 [PubMed: 8962108]
23. Asahi M et al. (2000) *Helicobacter pylori* CagA protein can be tyrosine phosphorylated in gastric epithelial cells. Journal of Experimental Medicine 191, 593–602 [PubMed: 10684851]
24. van Doorn LJ et al. (1998) Clinical relevance of the cagA, vacA, and iceA status of *Helicobacter pylori*. Gastroenterology 115, 58–66 [PubMed: 9649459]
25. Huang JQ et al. (2003) Meta-analysis of the relationship between cagA seropositivity and gastric cancer. Gastroenterology 125, 1636–1644 [PubMed: 14724815]
26. Parsonnet J et al. (1997) Risk for gastric cancer in people with CagA positive or CagA negative *Helicobacter pylori* infection. Gut 40, 297–301 [PubMed: 9135515]
27. Brandt S et al. (2005) NF-kappaB activation and potentiation of proinflammatory responses by the *Helicobacter pylori* CagA protein. Proceedings of the National Academy of Sciences of the United States of America 102, 9300–9305 [PubMed: 15972330]

28. Crabtree JE et al. (1995) *Helicobacter pylori* induced interleukin-8 expression in gastric epithelial cells is associated with CagA positive phenotype. Journal of Clinical Pathology 48, 41–45 [PubMed: 7706517]
29. Yamaoka Y et al. (1996) *Helicobacter pylori* cagA gene and expression of cytokine messenger RNA in gastric mucosa. Gastroenterology 110, 1744–1752 [PubMed: 8964399]
30. Backed S et al. (2001) Phosphorylation of tyrosine 972 of the *Helicobacter pylori* CagA protein is essential for induction of a scattering phenotype in gastric epithelial cells. Molecular Microbiology 42, 631–644 [PubMed: 11722731]
31. Franco AT et al. (2008) Regulation of gastric carcinogenesis by *Helicobacter pylori* virulence factors. Cancer Research 68, 379–387 [PubMed: 18199531]
32. Watanabe T. et al. (1998) *Helicobacter pylori* infection induces gastric cancer in mongolian gerbils. Gastroenterology 115, 642–648 [PubMed: 9721161]
33. Franco AT et al. (2005) Activation of beta-catenin by carcinogenic *Helicobacter pylori*. Proceedings of the National Academy of Sciences of the United States of America 102, 10646–10651 [PubMed: 16027366]
34. Sugimoto M et al. (2009) Gastric mucosal interleukin-17 and −18 mRNA expression in *Helicobacter pylori*-induced Mongolian gerbils. Cancer Science 100, 2152–2159 [PubMed: 19694753]
35. Sugimoto M et al. (2011) *Helicobacter pylori* outer membrane proteins on gastric mucosal interleukin 6 and 11 expression in Mongolian gerbils. Journal of Gastroenterology and Hepalology 26, 1677–1684
36. Nozaki K et al. (2002) Reversibility of heterotopic proliferative glands in glandular stomach of *Helicobacter pylori*-infected Mongolian gerbils on eradication. Japanese Journal of Cancer Research 93, 374–381 [PubMed: 11985786]
37. Cao X et al. (2004) Eradication of *Helicobacter pylori* induces apoptosis and inhibits proliferation of heterotopic proliferative glands in infected Mongolian gerbils. Cancer Science 95, 872–877 [PubMed: 15546504]
38. Shimizu N et al. (2000) Eradication diminishes enhancing effects of *Helicobacter pylori* infection on glandular stomach carcinogenesis in Mongolian gerbils. Cancer Research 60, 1512–1514 [PubMed: 10749114]
39. Cai X et al. (2005) *Helicobacter felis* eradication restores normal architecture and inhibits gastric cancer progression in C57BL/6 mice. Gastroenterology 128, 1937–1952 [PubMed: 15940628]
40. Tsukamoto T et al. (2013) *Helicobacter pylori* infection and gastric carcinogenesis in rodent models. Seminars in Lmmunopathology 35, 177–190
41. Freedberg DE, Abrams JA and Wang TC (2014) Prevention of gastric cancer with antibiotics: can it be done without eradicating *Helicobacter pylori*? Journal of the National Cancer Institute 106, dju148 [PubMed: 24925352]
42. Cao X et al. (2002) Earlier *Helicobacter pylori* infection increases the risk for the N-methyl-N-nitrosourea-induced stomach carcinogenesis in Mongolian gerbils. Japanese Journal of Cancer Research 93, 1293–1298 [PubMed: 12495468]
43. Nozaki K et al. (2003) Effect of early eradication on *Helicobacter pylori*-related gastric carcinogenesis in Mongolian gerbils. Cancer Science 94, 235–239 [PubMed: 12824915]
44. Ohnishi N et al. (2008) Transgenic expression of *Helicobacter pylori* CagA induces gastrointestinal and hematopoietic neoplasms in mouse. Proceedings of the National Academy of Sciences of the United States of America 105, 1003–1008 [PubMed: 18192401]
45. Hayakawa Y et al. (2013) Mouse models of gastric cancer. Cancers (Basel) 5, 92–130 [PubMed: 24216700]
46. Zhang W, Lu H and Graham DY (2014) An Update on *Helicobacter pylori* as the cause of Gastric Cancer. Gastrointestinal Tumors 1, 155–165 [PubMed: 26672968]
47. Hatakeyama M (2004) Oncogenic mechanisms of the *Helicobacter pylori* CagA protein. Nature Reviews. Cancer 4, 688–694 [PubMed: 15343275]
48. Higashi H et al. (2002) Biological activity of the *Helicobacter pylori* virulence factor CagA is determined by variation in the tyrosine phosphorylation sites. Proceedings of the National Academy of Sciences of the United States of America 99, 14428–14433 [PubMed: 12391297]

49. Satomi S et al. (2006) Relationship between the diversity of the cagA gene of *Helicobacter pylori* and gastric cancer in Okinawa, Japan. Journal of Gastroenterology 41, 668–673 [PubMed: 16933004]
50. Abe T et al. (2011) Impact of *Helicobacter pylori* CagA diversity on gastric mucosal damage: an immunohistochemical study of East-Asian-type CagA. Journal of Gastroenterology and Hepatology 26, 688–693 [PubMed: 21054521]
51. Matsunari O et al. (2012) Association between *Helicobacter pylori* virulence factors and gastroduodenal diseases in Okinawa, Japan. Journal of Clinical Microbiology 50, 876–883 [PubMed: 22189111]
52. Vilaichone RK et al. (2004) Molecular epidemiology and outcome of *Helicobacter pylori* infection in Thailand: a cultural cross roads. Helicobacter 9, 453–459 [PubMed: 15361085]
53. Matsuhisa T et al. (2015) Gastric mucosa in Mongolian and Japanese patients with gastric cancer and *Helicobacter pylori* infection. World Journal of Gastroenterology 21, 8408–8417 [PubMed: 26217093]
54. Xia Y et al. (2009) A comprehensive sequence and disease correlation analyses for the C-terminal region of CagA protein of *Helicobacter pylori*. PLoS ONE 4, e7736 [PubMed: 19893742]
55. Yamaoka Y et al. (1998) Variants of the 3' region of the cagA gene in *Helicobacter pylori* isolates from patients with different *H. pylori*-associated diseases. Journal of' Clinical Microbiology 36, 2258–2263 [PubMed: 9666002]
56. Yamaoka Y et al. (1999) Relationship between the cagA 3′ repeat region of *Helicobacter pylori*, gastric histology, and susceptibility to low pH. Gastroenterology 117, 342–349 [PubMed: 10419915]
57. Argent R et al. (2004) Determinants and consequences of different levels of CagA phosphorylation for clinical isolates of *Helicobacter pylori*. Gastroenterology 127, 514–523 [PubMed: 15300584]
58. Azunra T et al. (2002) Correlation between variation of the 3' region of the cagA gene in *Helicobacter pylori* and disease outcome in Japan. Journal of Infectious Diseases 186,1621–1630 [PubMed: 12447739]
59. Naito M et al. (2006) Influence of EPIYA-repeat polymorphism on the phosphorylation-dependent biological activity of *Helicobacter pylori* CagA. Gastroenterology 130, 1181–1190 [PubMed: 16618412]
60. Nagase L et al. (2015) Dramatic increase in SHP2 binding activity of *Helicobacter pylori* Western CagA by EPIYA-C duplication: its implications in gastric carcinogenesis. Scientific Reports 5, 15749 [PubMed: 26507409]
61. Yamaoka Y, Reddy R and Graham DY (2010) *Helicobacter pylori* virulence factor genotypes in children in the United States: clues about genotype and outcome relationships. Journal of Clinical Microbiology 48, 2550–2551 [PubMed: 20421443]
62. Atherton JC et al. (1995) Mosaicism in vacuolating cytotoxin alleles of *Helicobacter pylori*. Association of specific vacA types with cytotoxin production and peptic ulceration. Journal of Biological Chemistry 270, 17771–17777 [PubMed: 7629077]
63. Cover TL et al. (1994) Divergence of genetic sequences for the vacuolating cytotoxin among *Helicobacter pylori* strains. Journal of Biological Chemistry 269, 10566–10573 [PubMed: 8144644]
64. McClain MS et al. (2001) A 12-amino-acid segment, present in type s2 but not type s1 *Helicobacter pylori* VacA proteins, abolishes cytotoxin activity and alters membrane channel formation. Journal of Bacteriology 183, 6499–6508 [PubMed: 11673417]
65. Cover TL and Blanke SR (2005) *Helicobacter pylori* VacA, a paradigm for toxin multifunctionality. Nature Reviews. Microbiology 3, 320–332 [PubMed: 15759043]
66. Radin JN et al. (2014) Role of connexin 43 in *Helicobacter pylori* VacA-induced cell death. Infection and Immunity 82, 423–432 [PubMed: 24191302]
67. Menron AA et al. (2014) Vacuolating cytotoxin genotypes are strong markers of gastric cancer and duodenal ulcer-associated *Helicobacter pylori* strains: a matched case-control study. Journal of Clinical Microbiology 52, 2984–2989 [PubMed: 24920772]
68. Saxena A et al. (2011) Virulence attributes of *Helicobacter pylori isolates* & their association with gastroduodenal disease. Indian Journal of Medical Research 133, 514–520 [PubMed: 21623037]

69. Chonrvarin C et al. (2008) Prevalence of *Helicobacter pylori* vacA, cagA, cagE, iceA and babA2 genotypes in Thai dyspeptic patients. International Journal of Infectious Diseases 12, 30–36 [PubMed: 17548220]
70. Suginroto M and Yamaoka Y (2009) The association of vacA genotype and *Helicobacter pylori*-related disease in Latin American and African populations. Clinical Microbiology and Infection 15, 835–842 [PubMed: 19392900]
71. Gonzalez CA et al. (2011) *Helicobacter pylori* cagA and vacA genotypes as predictors of progression of gastric preneoplastic lesions: a long-term follow-up in a high-risk area in Spain. American Journal of Gastroenterology 106, 867–874 [PubMed: 21285949]
72. Rhead JL et al. (2007) A new *Helicobacter pylori* vacuolating cytotoxin determinant, the intermediate region, is associated with gastric cancer. Gastroenterology 133, 926–936 [PubMed: 17854597]
73. Ogiwara H et al. (2009) Role of deletion located between the intermediate and middle regions of the *Helicobacter pylori* vacA gene in cases of gastroduodenal diseases. Journal of Clinical Microbiology 47, 3493–3500 [PubMed: 19726606]
74. Bakhti SZ et al. (2016) Relevance of *Helicobacter pylori* vacA 3′-end region polymorphism to gastric cancer. Helicobacter 21, 305–316 [PubMed: 26612250]
75. Hussein NR et al. (2008) Differences in virulence markers between *Helicobacter pylori* strains from Iraq and those from Iran: potential importance of regional differences in *H. pylori*-associated disease. Journal of Clinical Microbiology 46, 1774–1779 [PubMed: 18353934]
76. Basso D et al. (2008) Clinical relevance of *Helicobacter pylori* cagA and vacA gene polymorphisms. Gastroenterology 135, 91–99 [PubMed: 18474244]
77. Yordanov D et al. (2012) Significance of *Helicobacter pylori* vacA intermediate region genotyping – a Bulgarian study. Diagnostic Microbiology and Infectious Disease 74, 253–257 [PubMed: 22951332]
78. Ogiwara H, Graham DY and Yamaoka Y (2008) vacA i-region subtyping. Gastroenterology 134, 1267; author reply 1268 [PubMed: 18395110]
79. Yamaoka Y et al. (1998) Relationship of vacA genotypes of *Helicobacter pylori* to cagA status, cytotoxin production, and clinical outcome. Helicobacter 3, 241–253 [PubMed: 9844065]
80. Backed S, Clyne M and Tegtmeyer N (2011) Molecular mechanisms of gastric epithelial cell adhesion and injection of CagA by *Helicobacter pylori*. Cell Communication and Signaling 9, 28 [PubMed: 22044679]
81. Yamaoka Y et al. (2002) Importance of *Helicobacter pylori* oipA in clinical presentation, gastric inflammation, and mucosal interleukin 8 production. Gastroenterology 123, 414–424 [PubMed: 12145793]
82. Yamaoka Y et al. (2006) *Helicobacter pylori* outer membrane proteins and gastroduodenal disease. Gut 55, 775–781 [PubMed: 16322107]
83. Liu J et al. (2013) Association of presence/absence and on/off patterns of *Helicobacter pylori* oipA gene with peptic ulcer disease and gastric cancer risks: a meta-analysis. BMC Infectious Diseases 13, 555 [PubMed: 24256489]
84. Sheu BS et al. (2003) Host gastric Lewis expression determines the bacterial density of *Helicobacter pylori* in babA2 genopositive infection. Gut 52, 927–932 [PubMed: 12801945]
85. Moonens K et al. (2016) Structural insights into polymorphic ABO glycan binding by *Helicobacter pylori*. Cell Host & Microbe 19, 55–66 [PubMed: 26764597]
86. Rad R et al. (2002) The *Helicobacter pylori* blood group antigen-binding adhesin facilitates bacterial colonization and augments a nonspecific immune response. Journal of Immunology 168, 3033–3041
87. Hill AB (1965) The environment and disease: association or causation? Proceedings of the Royal Society of Medicine 58, 295–300 [PubMed: 14283879]
88. Kikuchi S (2002) Epidemiology of *Helicobacter pylori* and gastric cancer. Gastric Cancer 5, 6–15 [PubMed: 12021854]
89. Hanada K et al. (2014) *Helicobacter pylori* infection introduces DNA double-strand breaks in host cells. Infection and Immunity 82, 4182–4189 [PubMed: 25069978]

90. Shiotani A, Cen P and Graham DY (2013) Eradication of gastric cancer is now both possible and practical. Seminars in Cancer Biology 23, 492–501 [PubMed: 23876852]
91. Okazaki IM et al. (2003) Constitutive expression of AID leads to tumorigenesis. Journal of Experimental Medicine 197, 1173–1181 [PubMed: 12732658]
92. Shimizu T et al. (2015) Molecular pathogenesis of *Helicobacter pylori*-related gastric cancer. Gastroenterology Clinics of North America 44, 625–638 [PubMed: 26314672]
93. Hollstein M et al. (1991) p53 mutations in human cancers. Science 253, 49–53 [PubMed: 1905840]
94. Matsumoto Y et al. (2007) *Helicobacter pylori* infection triggers aberrant expression of activation-induced cytidine deaminase in gastric epithelium. Natural Medicines 13, 470–476
95. Toller IM et al. (2011) Carcinogenic bacterial pathogen *Helicobacter pylori* triggers DNA double-strand breaks and a DNA damage response in its host cells. Proceedings of the National Academy of Sciences of the United States of America 108, 14944–14949 [PubMed: 21896770]
96. Xu Y and Price BD (2011) Chromatin dynamics and the repair of DNA double strand breaks. Cell Cycle 10, 261–267 [PubMed: 21212734]
97. Mantovani A (2010) Molecular pathways linking inflammation and cancer. Current Molecular Medicine 10, 369–373 [PubMed: 20455855]
98. Nardone G et al. (2007) *Helicobacter pylori* and epigenetic mechanisms underlying gastric carcinogenesis. Digestive Diseases 25, 225–229 [PubMed: 17827945]
99. Maekita T et al. (2006) High levels of aberrant DNA methylation in *Helicobacter pylori*-infected gastric mucosae and its possible association with gastric cancer risk. Clinical Cancer Research 12, 989–995 [PubMed: 16467114]
100. Fischle W, Wang Y and Allis CD (2003) Histone and chromatin cross-talk. Current Opinion in Cell Biology 15, 172–183 [PubMed: 12648673]
101. Barbarotto E, Schmittgen TD and Calin GA (2008) MicroRNAs and cancer: profile, profile, profile. International Journal of Cancer 122, 969–977 [PubMed: 18098138]
102. Zhang Z et al. (2008) miR-21 plays a pivotal role in gastric cancer pathogenesis and progression. Laboratory Investigation 88, 1358–1366 [PubMed: 18794849]
103. Petrocca F et al. (2008) E2F1-regulated microRNAs impair TGFbeta-dependent cell-cycle arrest and apoptosis in gastric cancer. Cancer Cell 13, 272–286 [PubMed: 18328430]
104. Nagata N et al. (2014) Enhanced expression of activation-induced cytidine deaminase in human gastric mucosa infected by *Helicobacter pylori* and its decrease following eradication. Journal of Gastroenterology 49, 427–435 [PubMed: 23591766]
105. Shiotani A et al. (2012) Eradication of *H. pylori* did not improve abnormal sonic hedgehog expression in the high risk group for gastric cancer. Digestive Diseases and Sciences 57, 643–649 [PubMed: 21953141]
106. Shiotani A et al. (2012) *H. pylori* eradication did not improve dysregulation of specific oncogenic miRNAs in intestinal metaplastic glands. Journal of Gastroenterology 47, 988–998 [PubMed: 22382634]
107. Take S et al. (2007) Baseline gastric mucosal atrophy is a risk factor associated with the development of gastric cancer after *Helicobacter pylori* eradication therapy in patients with peptic ulcer diseases. Journal of Gastroenterology 42 (Suppl 17), 21–27 [PubMed: 17238021]
108. Shiotani A, Haruma K and Graham DY (2014) Metachronous gastric cancer after successful *Helicobacter pylori* eradication. World Journal of Gastroenterology 20, 11552–11559 [PubMed: 25206262]
109. Graham DY (2014) *Helicobacter pylori* eradication and metachronous gastric cancer. Clinical Gastroenterology and Hepatology 12, 801–803 [PubMed: 24211292]
110. Shiotani A, Matsueda A and Graham DY (2015) Changing the natural history of metachronous gastric cancer after *H. pylori* eradication. Japanese Journal of Helicobacter Research 16, 52–60
111. Yoon SB et al. (2014) Effect of *Helicobacter pylori* eradication on metachronous gastric cancer after endoscopic resection of gastric tumors: a meta-analysis. Helicobacter 19, 243–248 [PubMed: 25056262]

112. Comfort MW (1951) Gastric acidity before and after development of gastric cancer: its etiologic, diagnostic and prognostic significance. Annals of Internal Medicine 34, 1331–1348 [PubMed: 14838496]

113. Forsythe SJ et al. (1988) Nitrate- and nitrite-reducing bacteria in the achlorhydric stomach. Journal of Medical Microbiology 25, 253–259 [PubMed: 3357192]

114. Osato MS et al. (1998) Microflora of gastric biopsies from patients with duodenal ulcer and gastric cancer: a comparative study of patients from Korea, Colombia, and the United States. Digestive Diseases and Sciences 43, 2291–2295 [PubMed: 9790468]

115. Rugge M et al. (2012) Autoimmune gastritis: histology phenotype and OLGA staging. Alimentaty Pharmacology & Therapeutics. 1460–1466

116. Gaddy JA et al. (2013) High dietary salt intake exacerbates *Helicobacter pylori*-induced gastric carcinogenesis. Infection and Immunity 81, 2258–2267 [PubMed: 23569116]

117. Graham DY, Shiotani A and El-Zimaity HM (2006) Chromoendoscopy points the way to understanding recovery of gastric function after *Helicobacter pylori* eradication. Gastrointestinal Endoscopy 64, 686–690 [PubMed: 17055857]

118. Chang WJ et al. (2014) Inflammation-related factors predicting prognosis of gastric cancer. World Journal of Gastroenterology 20, 4586–4596 [PubMed: 24782611]

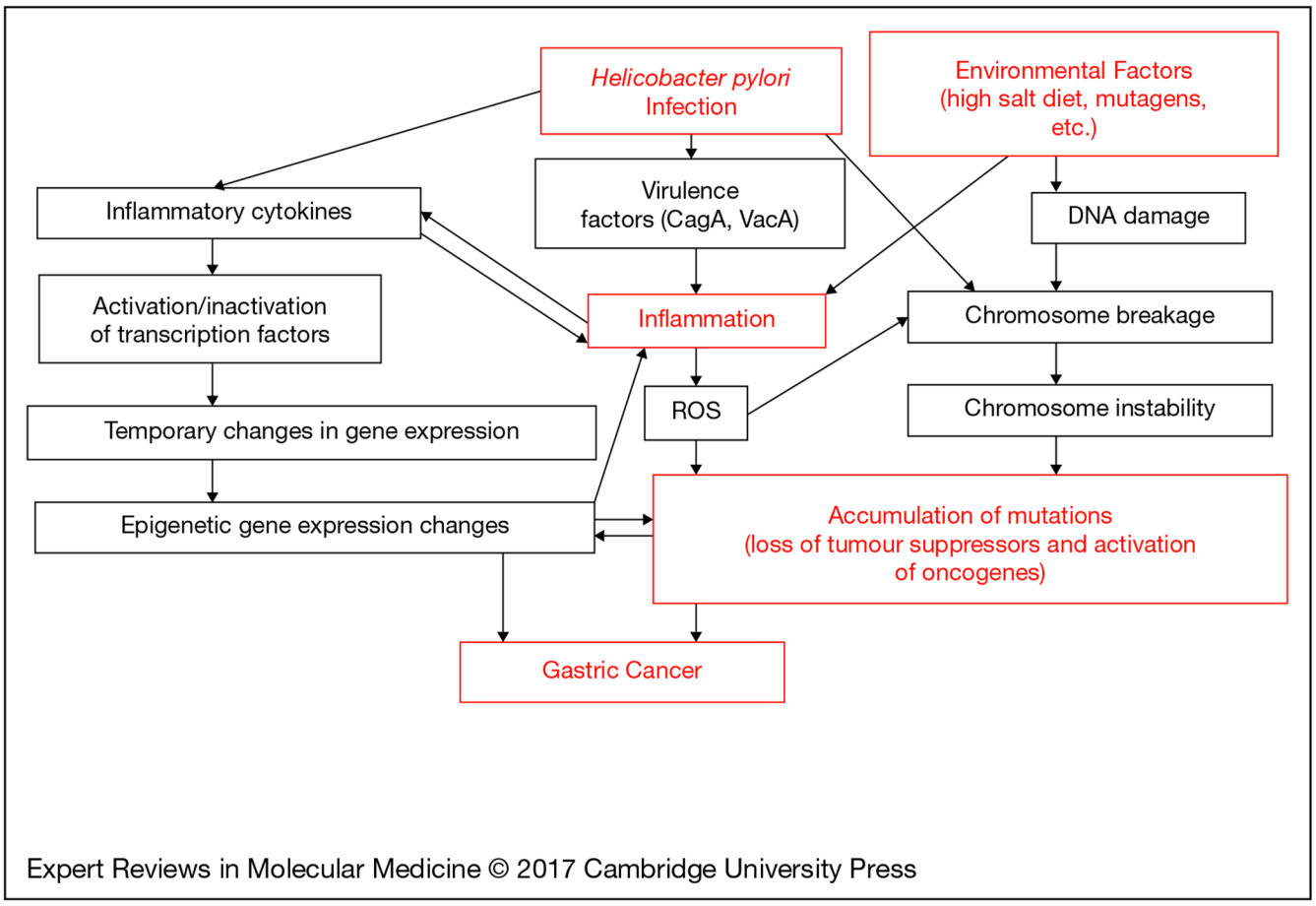

FIGURE 1.

Role of inflammation in the pathogenesis of *Helicobacter pylori*-associated gastric carcinogenesis. Adapted from Hanada and Graham (Ref. 17), with permission.

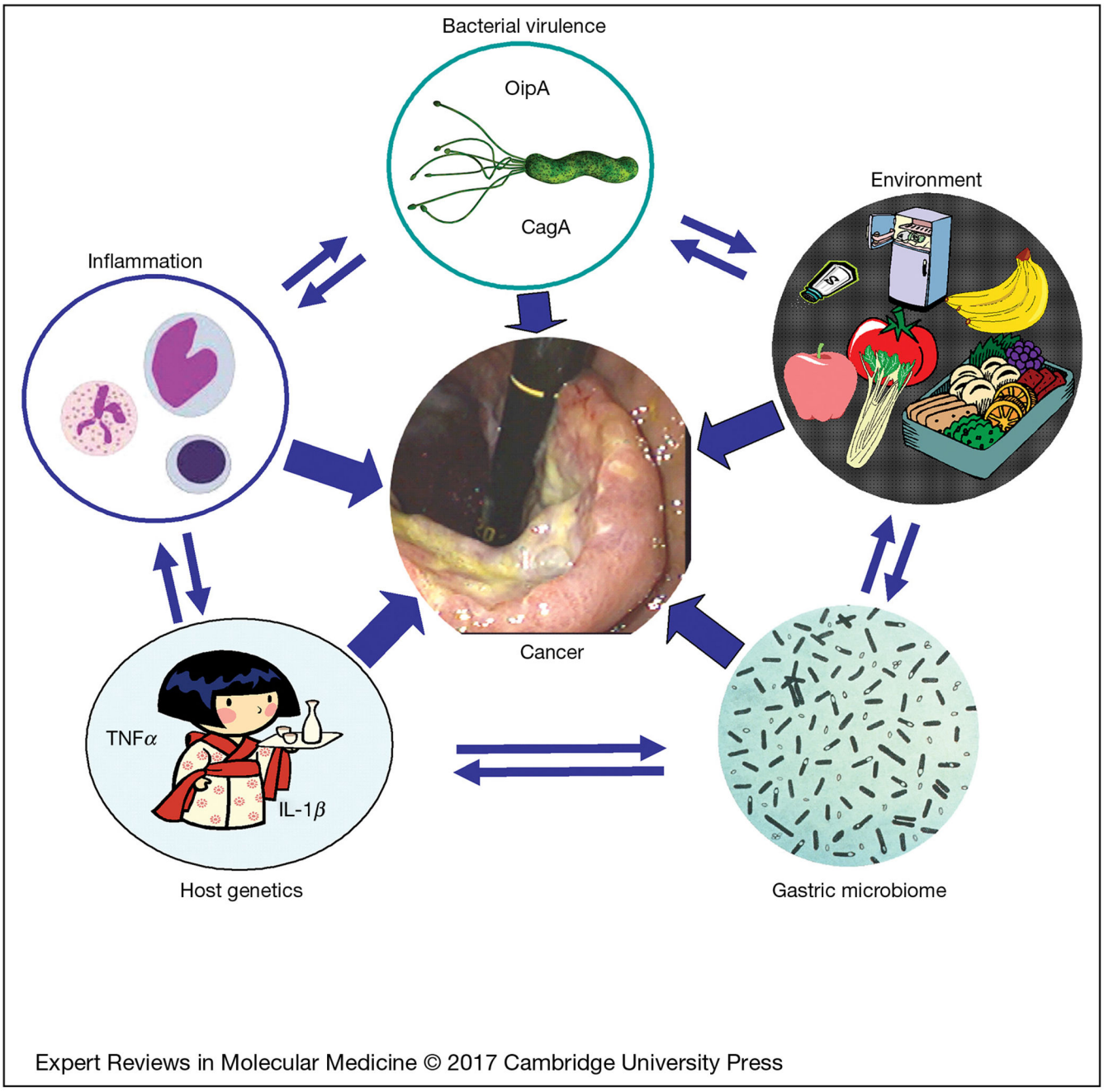

FIGURE 2.
The major factors in the multifactorial pathogenesis of gastric cancer.

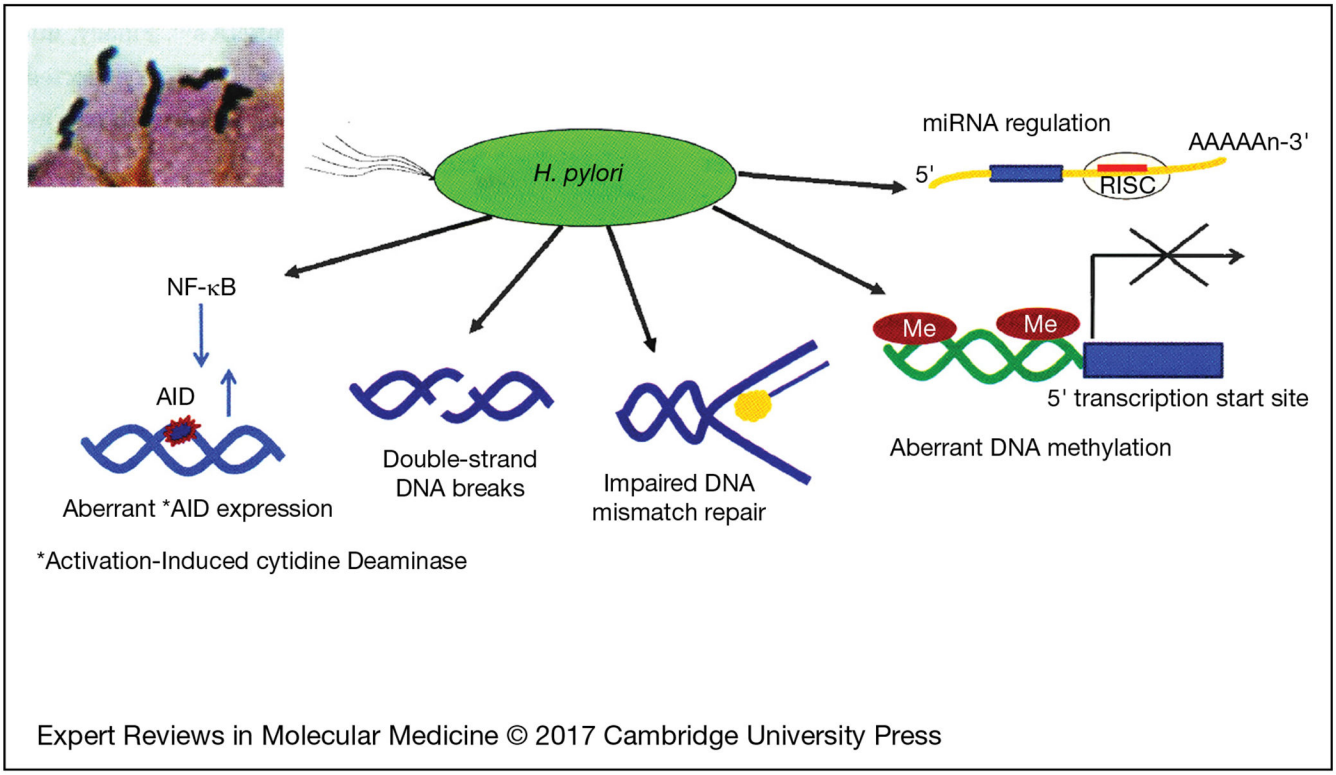

FIGURE 3.

Summary of inflammation-host-bacteria interactions involved in *H. pylori*-associated gastric cancer. Adapted from Graham (Ref 8), with permission.

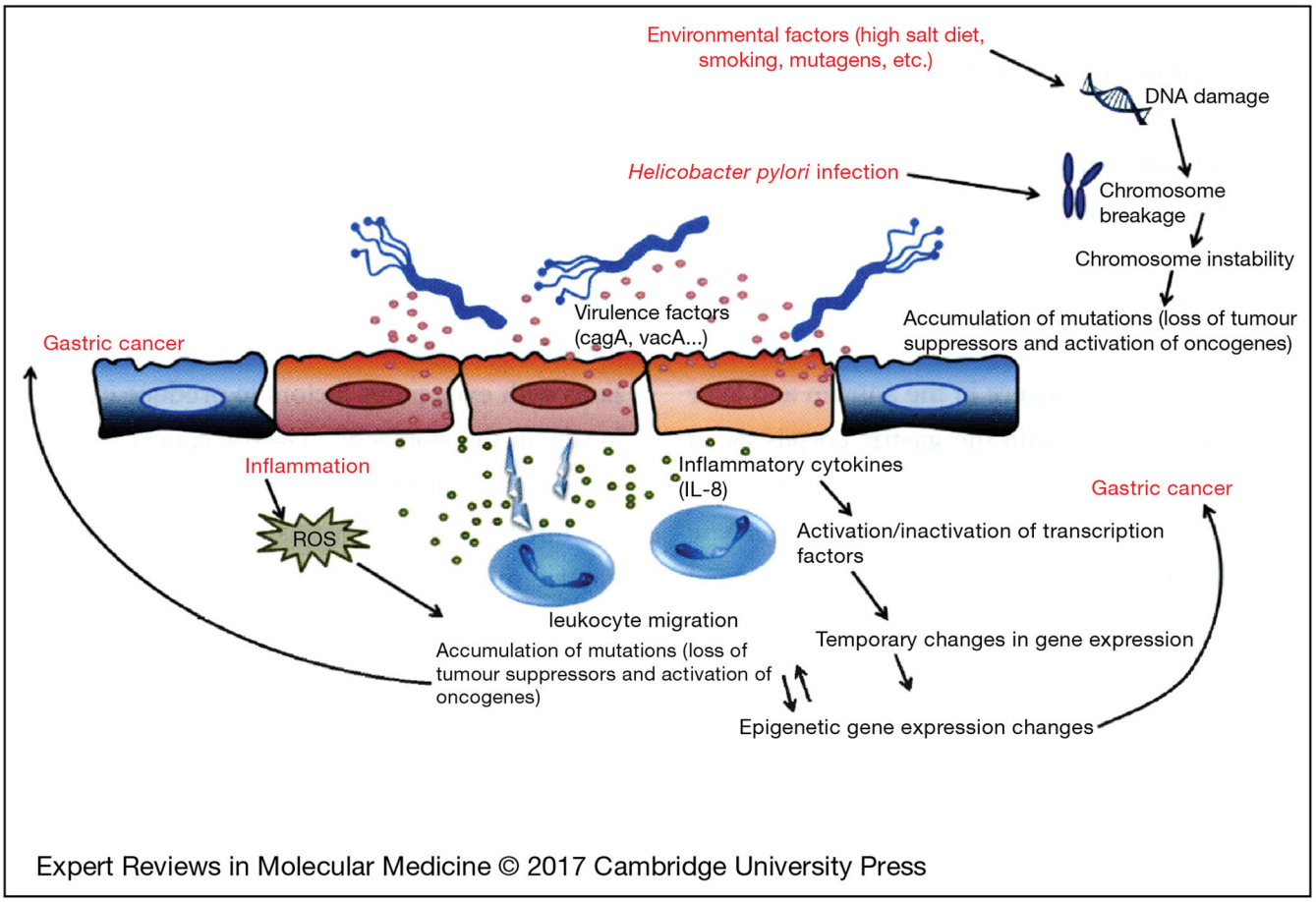

FIGURE 4.

The role of *H. pylori* contributing to genetic instability. Adapted from Shiotani et al. (Ref. 90), with permission.

TABLE 1.

PUTATIVE VIRULENCE FACTORS POSSIBLY RELATED TO CLINICAL OUTCOMES

Gene or region	Protein	*H. pylori* virulence genes type	
		High virulent	**Less virulent**
cag PAI	CagA and T4SS	Complete	Incomplete or absent
*cag*A	CagA	Positive	Negative
		East-Asian-type CagA	Western-type CagA
		Multiple repeats (e.g. ABCC, ABCCC, ABBD)	Single repeat
*vac*A	VacA	s1, m1, i1, c1, d1 forms	S2, m2, i2, c2, d2 forms
*bab*A	BabA	Present	Absent
*oip*A	OipA	On	Off

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