Host-Environment Interactions: Their Impact on Progression from Gastric Inflammation to Carcinogenesis and on Development of New Approaches to Prevent and Treat Gastric Cancer

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Abstract

Revelation of the connection between Helicobacter pylori infection and gastric adenocarcinoma has prompted new investigations pertaining to its basic and clinical aspects. H. pylori–induced persistent and uncontrolled gastric inflammation nearly always precedes the development of cancer and is instrumental in initiating a multistep process leading to carcinogenesis. Despite initial optimism about the potential of combination anti–H. pylori therapy to ultimately eradicate gastric adenocarcinoma, recent investigations suggest its use should be targeted and tailored to a selected patient group considering the multifaceted role of H. pylori in disease and the disease heterogeneity of gastric adenocarcinoma. The clinical spectrum of H. pylori infection ranges from asymptomatic gastritis and peptic ulcer to gastric malignancies. The occurrence of one versus another is the result of differences in the magnitude of gastritis, and the current disease paradigm suggests gastric inflammation is common to all H. pylori–associated gastroduodenal diseases. Therefore, the host inflammatory responses to environmental triggers, rather than to bacteria or environmental factors per se, would dictate the variable outcomes of H. pylori infection. Putative factors that are expected to play an important role in stimulating inflammatory pathways and modulating the cross-talk between host and environment are age at the time of infection, environmental cofactors, H. pylori virulence, and host genetics. Elucidation of the intimate relationship between host-environment interaction and gastric inflammation, although currently a formidable task, is essential in the development of new prevention and treatment strategies. Such knowledge might provide clues that allow more accurate prediction of variable outcomes of gastric inflammation and appropriate adjustment of treatment strategies, and might open up novel areas for studying gastric carcinogenesis. The evolving new technologies, such as microarray, proteomic, and functional genomic analyses, promise to shed new light on the immense complexity of the presumed host-environment interactions and will reveal more useful markers for the diagnosis and prognosis of gastric adenocarcinoma.

Introduction

Despite its decline in incidence, gastric adenocarcinoma remains a worldwide disease with a dismal prognosis (1). It is noteworthy that gastric adenocarcinoma is heterogeneous with respect to anatomic location, histologic subtypes, and etiologic factors. Anatomically, gastric adenocarcinoma can grossly be split into two major types, cardia and noncardia gastric adenocarcinomas. The cardia cancers share important features with esophageal and gastroesophageal junction adenocarcinomas and these features distinguish cardia from “noncardia” gastric adenocarcinoma, found more commonly in the distal stomach. Cardia gastric adenocarcinoma patients are younger at the time of diagnosis, mostly male, are more likely to use tobacco and alcohol, more likely to have concomitant hiatal hernia, less likely to have chronic gastritis, and more likely to have a diffuse type cancer. The incidence of cardia cancer (in contrast to that of noncardia gastric adenocarcinoma) is increasing (2).

Histologically, gastric adenocarcinoma may be subdivided into intestinal and diffuse types. The intestinal type (also known as the “epithelial type”) predominates in high-risk populations, is more frequently found in the elderly, and is characterized by a histologic pattern similar to that of large bowel adenocarcinoma. The diffuse type of gastric adenocarcinoma is less common, occurring relatively more frequently in low-risk populations and mostly in younger or “blood group A” people. Different precancerous lesions probably exist for these two types inasmuch as the intestinal type of gastric adenocarcinoma follows the proposed sequential changes from gastritis, intestinal metaplasia, and dysplasia to cancer (3). Moreover, profiles of genetic alterations differ in relation to its anatomic locations and histologic subtypes of gastric adenocarcinoma (4).

In terms of etiologic factors, the major environmental risks for gastric adenocarcinoma are traditionally linked to diet, smoking, and occupational exposure. Recently, abundant epidemiologic data and animal studies have documented that Helicobacter pylori is the major determinant of environmental risk for noncardia gastric adenocarcinoma (5). However, a small portion of gastric adenocarcinoma cases is associated with EBV infection (6). Distinct clinical and epidemiologic differences between cancers arising from different locations within the stomach or cancers of different histologic types suggest these cancers may in fact represent different disease entities. These characteristics are germane to the discussion of...
gastric carcinogenesis. For simplicity, the following discussion centers mainly on noncardia gastric adenocarcinoma.

From Inflammation to Carcinogenesis

The infectious and noninfectious generation of chronic injury and irritation initiates an inflammatory response. Recent data have expanded the concept that inflammation is a critical component of tumor development. The notion that inflammation has a relationship to cancer started with the seminal publication by Virchow in 1863 that proposed that cancer originated at sites of chronic inflammation (7). A growing body of epidemiologic and laboratory evidence has emerged showing that long-standing inflammation promotes tumor development, growth, and progression (8). The new paradigm suggests that chronic inflammation is a risk or prerequisite factor for the development of a number of human malignancies, including liver, colon, stomach, bladder, cervix, ovary, and lung carcinomas (7, 8). Inflammation-induced injury may compromise tissue integrity and drive the multistage process of carcinogenesis by altering targets and pathways that are crucial to normal tissue homeostasis. Potential mechanisms include generation of mutagenic reactive oxygen and nitrogen species and elaboration of cytokines and growth factors that favor tumor cell growth (8). Reactive oxygen and nitrogen species might damage cells and DNA. Proliferation of epithelial cells in the milieu of oxyradical-induced injury may result in conversion of DNA damage to mutations (genetic alterations) or nonmutational silencing of genes at the transcriptional level (epigenetic alterations). Degrees and spectra of genetic and epigenetic alterations vary in different tumors but provide clues to pathways with a growth and/or antiapoptotic advantage. Inflammatory alterations may also promote growth, expansion, and invasion of tumors even without further genetic mutations or epigenetic alterations, and therefore inflammatory alterations may be characterized as ‘perigenetic alterations’ of neoplastic cells (9). For example, cyclooxygenase-2 is frequently up-regulated in various types of tumors; however, the gene coding cyclooxygenase-2 protein is neither mutated nor epigenetically altered. In addition, the inflammatory microenvironment is not inert but active in tumor progression and metastasis. In fact, stromal cells and their cytokines coordinate critical pathways that play important roles in tumor invasion and metastasis (10). A more recent finding is that the presence of an inflammatory response identifies patients with more aggressive disease and may also compromise the pharmacodynamics of anticancer drugs (11). Taken together, the process of tumorigenesis is dependent on the inflammatory microenvironment and its communication with neoplastic cells. Such tumor-stromal interaction may provide a rich new source of important targets for cancer diagnosis, therapy, and prognosis. It is reasonable to speculate that elucidation of the inflammation-based carcinogenesis would open up new opportunities for cancer management. Notably, the recent identification of cyclooxygenase-2 inhibitors as a potential cancer chemopreventive agent supports this speculation.

Gastric Inflammation: A Common Denominator of H. pylori Infections with Different Outcomes

In the last two decades, studies of gastric adenocarcinoma focused on the H. pylori infectious process. It was estimated that half of the world population harbors H. pylori and about 337,800 gastric adenocarcinoma deaths were attributable to H. pylori infection in the year 2000 (12). H. pylori-mediated events, such as production of reactive oxygen species, activation of growth factors and cytokines, and alterations of signal transduction processes, are potential components of risk for gastric adenocarcinoma (13, 14). Further evidence linking H. pylori to gastric adenocarcinoma is provided by pathologic studies of preneoplastic and neoplastic tissues, epidemiologic studies, and studies using animal models (15). Whereas there is evidence to support the association between H. pylori and gastric adenocarcinoma, only a subset, ~1% to 2%, of infected individuals develops gastric malignancies. About 80% of H. pylori–infected individuals have asymptomatic gastritis, 10% to 15% have peptic ulcer, and a very small proportion develop gastric mucosa–associated lymphoid tissue lymphoma (15). The diversity of disease phenotypes of H. pylori infection is related to the extent and severity of gastritis, which leads to different variation in the amount of acid secretion and thus the permissive tumor milieu for disease to develop. For example, peptic ulcer is closely associated with antral-predominant gastritis and increased acid secretion; gastric adenocarcinoma follows pangastritis and gastric atrophy, which may reduce acid secretion, whereas gastric mucosa–associated lymphoid tissue lymphoma is linked to lymphocyte-predominant follicular gastritis (16). Moreover, the escalating rates of gastroesophageal reflux diseases and cardio gastric adenocarcinoma and decreasing rates of noncardia gastric adenocarcinoma in Western countries are likely due to changes in H. pylori infection prevalence and density coupled with differences in the anatomic distribution of gastritis (17). Because gastric inflammation is a common precursor of various gastroduodenal diseases, identification of the factors that underlie gastric inflammation is crucial not only for a better understanding of gastric carcinogenesis but also for future prevention and treatment of H. pylori–related diseases.

Disturbances in the Delicate Balance between Host and Environment Determine the Outcomes of Gastric Inflammation

The fundamental role of H. pylori in gastric inflammation and gastric adenocarcinoma and the broad clinical spectrum of H. pylori–mediated gastrointestinal disease have aroused interest in factors that influence the course of H. pylori infection. Factors that are expected to contribute to inflammatory pathway stimulation and affect risk are age at diagnosis of H. pylori infection, environmental cofactors, H. pylori strain variability, and host genetics (13, 18). As shown in epidemiologic analyses, the earlier that people become infected, the greater the probability that infection will progress to gastric atrophy and gastric adenocarcinoma (19). This phenomenon is also seen in other infection-related malignancies that showed age of exposure to common childhood infection, rather than only pathogen or socioeconomic status, affects disease incidence (20). These studies imply environmental factors may also modify the developing immune system in an age-dependent manner (19, 20). Several traditional risk factors, such as high-salt/low-vegetable diets and smoking, are associated with proinflammatory alterations of gastric mucosa and thus affect the extent and severity of gastric inflammation (21).

Mounting evidence suggests that strain variations are central to pathogenesis of infectious diseases and may in part explain different outcomes of H. pylori infection (22). Most strains of H. pylori can be divided into two distinct phenotypes on the basis of the presence or absence of the cag pathogenicity island, a large chromosomal region that encodes virulence genes, including cytotoxin-associated gene A (cagA). Strains bearing cagA are particularly virulent and result in significant perturbation of proliferation and apoptosis of gastric epithelial cells (23). People infected with cagA–positive H. pylori are more likely to have noncardia gastric adenocarcinoma but less prone to cardio gastric adenocarcinoma and reflux esophagitis (24). The combination of various virulence genes, including cagA, vcaA, and babA,
could further add to the risk of gastric inflammation and gastric adenocarcinoma (25). Despite marked progress in defining *H. pylori* genotypes, recent investigations have shown that mice with different genetic backgrounds may manifest different gastrointestinal inflammation sequels and diseases (26). Furthermore, studies of twins, familial clustering, ethnic differences, and HLA genes have also provided strong evidence that host genetic factors play a dominant role in determining the spectrum of gastritis and disease expression (27, 28). Several types of polymorphisms in the human genome are considered to be responsible for such interindividual differences. Of these, the most likely candidates are single nucleotide polymorphisms in the promoter regions of various genes. Single nucleotide polymorphisms might be involved in differential *in vitro* expression of the respective gene products. These inherited genotypes may exert their actions at multiple levels of the multistage carcinogenesis process through differences in carcinogenic metabolism, inflammatory responses, DNA repair, and oncogenes or tumor suppressor genes (29). Of significance in this regard is the recent recognition that interleukin-1β variants modulate the risk of gastric adenocarcinoma (30) and glutathione S-transferase null genotypes are linked to gastric mucosa-associated lymphoid tissue lymphoma (31). These results indicate the risk associated with *H. pylori* infection may be influenced by the inflammatory responses of the individual host, with the higher risk in those genetically predisposed to a strong response.

Although each individual factor could modify the risk of gastric adenocarcinoma, the above-mentioned factors do not act independently and are interrelated. Preliminary work suggests that dietary modulation of expression levels of certain cytokines in healthy human subjects may be genotype dependent (20). It stands to reason that an understanding of how genetic factors interact with each other and the environment will increase the sensitivity and specificity of techniques for predicting response to *H. pylori* infection. Recently, Figueiredo et al. (32) evaluated the bacteria infecting gastric adenocarcinoma patients and host genotypes and found the highest risk of gastric adenocarcinoma occurred in those carrying bacterial strains with high virulence (*cagA* and *vacA*) together with host high-risk genotypes (*IL-1β*). Another study investigated the combined effects of host and environment and showed the synergism between smoking and cytokine genotypes in enhancing the risk of gastric adenocarcinoma (33). Taken together, the magnitude of host response to environmental triggers, rather than to bacteria or environmental factors per se, confers susceptibility to or protection against gastric adenocarcinoma. This suggests that a delicate balance exists between host and environment, and that this balance provides a conceptual framework for understanding the influence of genetic and environmental factors on disease progression and the association between genetic susceptibility and inflammatory responses to *H. pylori* and gastric adenocarcinoma. This conceptual framework is depicted in Fig. 1. The study of the interplay between host and environment will not only provide further insights into the pathogenesis of gastric adenocarcinoma but will also lead to identification of markers having diagnostic and/or prognostic value in defining risk and targeting *H. pylori* eradication in high-risk individuals.

### Chemoprevention of Gastric Adenocarcinoma by Eradication of *H. pylori*, Anti-inflammatory Agents, and Antioxidants

The recognition that *H. pylori*-induced persistent and uncontrolled gastric inflammation is the basis for ensuing carcinogenesis has profound implications for the prevention of gastric adenocarcinoma. By making appropriate lifestyle and dietary changes, a variety of anti-inflammatory effects can be produced, which should attenuate inflammation-induced risk for gastric adenocarcinoma. In a trial of antibiotics and dietary supplements for prophylaxis of gastric dysplasia in Columbia, Correa et al. (34) showed that eradication of *H. pylori* infection or dietary supplementation with ascorbic acid and/or β-carotene could induce regression of precancerous lesions in patients with intestinal metaplasia and/or multifocal atrophic gastritis. The first randomized clinical trial of *H. pylori* eradication treatment, with gastric adenocarcinoma as an outcome, has recently been reported (35). Wong et al. found that the incidence of gastric adenocarcinoma development at the population level was similar in participants receiving *H. pylori* eradication treatment and those receiving placebo during a 7.5-year period in a high-risk region of China. However, in the subgroup of *H. pylori* carriers without precancerous lesions, eradication of *H. pylori* significantly decreased the development of gastric adenocarcinoma (34). Although certain caveats exist, such as underpowered statistics and insufficient period of follow-up, and this trial was too small to show an overall effect (36), the following lessons can be derived judiciously from this study: (a) To prevent *H. pylori*-related cancer, it is crucial to treat infection early in its course. Precancerous lesions such as intestinal metaplasia and gastric dysplasia were irreversible in this trial. (b) Validation of chemopreventive effects of *H. pylori* eradication may require the development of more sensitive assays to measure gastric inflammation. Appropriate biomarkers for clarification of severity of gastritis are essential to sort out those who might benefit from chemoprevention. The sensitivity and specificity of current serologic tests including assays of pepsinogen and gastrin are limited, and the risk profiles based on these tests are not satisfactory for gastric adenocarcinoma screening. Further researches to find new markers needed for diagnosis and prognosis are warranted. (c) Despite their promise, however, anti-*H. pylori* therapies cannot induce regression of advanced precursor lesions. Combinations of other chemopreventive agents such as dietary supplementation with ascorbic acid and β-carotene may be beneficial. However, the preliminary results from Correa and colleagues showed that combination of anti-*H. pylori* therapy with β-carotene or vitamin C did not increase the regression rate of precancerous lesions as compared with β-carotene or vitamin C alone (37). The intrinsic role of cyclooxygenase-2 in inflammation, angiogenesis, and tumor progression and its close association with *H. pylori* infection and gastric adenocarcinoma make nonsteroidal anti-inflammatory drugs promising agents (38). It is hoped that these agents will inhibit the neoplastic process either alone or in combination with other regimens. Nevertheless, the recent documentation of increased risk of cardiovascular events in patients taking rofecoxib makes long-term use of cyclooxygenase-2 inhibitors carry potential risks and tempers this hope (39). Proper clinical trials in specific patient populations are needed to resolve the issue of balance between the risks and benefits of different chemoprevention policies.

### Technological Advances Have Shed Light on Investigations of Complex Cross-talk between Host and Pathogen

As noted above, the current disease paradigm for the manifestation of *H. pylori*-related gastric adenocarcinoma involves genetic factors, lifestyle, and environmental exposure. Assessment of host-environment interaction might provide clues to allow more accurate prediction of variable outcomes of gastric inflammation and appropriate adjustment of treatment strategies, as well as to indicate novel areas for future studies of gastric carcinogenesis. In this regard, the...
introduction of new technologies, such as microarrays that can measure genome-wide expression of the host responses to environmental stimuli, provides a rapid, technically straightforward approach and promises to shed new light on the immense complexity of the presumed host-environment interactions (40). Among the recent important contributions relating to the host response to \textit{H. pylori}, global gene expression has been shown in \textit{H. pylori}, whether interacting with host cells \textit{in vitro}, in animal models, or in infected tissues (41-45). These studies delineate the cross-talk between the host and \textit{H. pylori}. Additional high throughput methods to investigate the bidirectional relationship include proteomics and functional genomic technologies such as RNA interference (46). Some promising results from investigations using proteomics to uncover novel immunogenic proteins have been reported (47, 48). These studies might enhance understanding of disease pathogenesis and facilitate the development of effective biomarkers for diagnosis, prevention, and treatment.

Figure 1. A conceptual framework to explain why only certain \textit{H. pylori}–infected patients develop gastric cancer. The quality and quantity of gastric inflammation due to interaction of host and environmental factors determine the different outcomes of \textit{H. pylori}–infected individuals.
Conclusion

Previous studies have suggested gastric adenocarcinoma is clinically detectable at an earlier stage, surgically and endoscopically curable, chemotherapeutically treatable, and epide-miologically preventable. Despite dramatic improvement in the ability to detect early gastric adenocarcinoma by endoscopy, this is an invasive procedure and population screening by this procedure is only feasible in affluent and high-risk countries such as Japan. The cure rate of patients with advanced gastric adenocarcinoma remains low and morbidity remains high although remarkable improvement in surgical techniques and chemotherapy has been made. Prevention of gastric adenocar-cinoma is potentially feasible through the eradication of H. pylori infection and avoidance of adverse lifestyles, but identification of high-risk populations is a prerequisite for the development of effective programs, although at present not practical. Therefore, gastric adenocarcinoma still poses an important public health problem, and knowledge of its pathogenesis and tumor biology is essential in designing future strategies for prevention and therapy.

To increase the effectiveness of these diagnostic, preventive, and therapeutic strategies, elucidation of the pathogenesis of gastric adenocarcinoma is mandatory. However, such an understanding is complicated by the fact that it is not a single disease but has many clinical and histologic manifestations. The proposal of a multistage model of carcinogenesis and the paradigm shift to H. pylori infection and gastric inflammation as central components have offered researchers testable hypotheses by which critical components of gastric carcinogenesis may be found. Technical advances such as microarrays, proteomics, and functional genomics coupled with complete deciphering of the human and H. pylori genome sequences herald a new era in gastric adenocarcinoma research. These endeavors have fueled optimism that we will eventually better understand this devastating disease. As the process of inflammation in the stomach and pathogenesis become better defined, more specific biomarkers and therapeutic targets will be identified, creating new opportunities to provide a more accurate molecular classification of disease, thus offering individuals a better prognostic evaluation for prevention and perhaps permit more specific, targeted medical and surgical treatments.

References

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