

Helicobacter Pylori And Gastric Carcinogenesis

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ABSTRACT Gastric cancer is the fourth most common cancer worldwide, with a frequency that varies greatly across different geographic areas. The Lauren classification of gastric carcinomas recognizes the intestinal and diffuse types that differ substantially in epidemiology and pathogenesis. The most important etiological factor associated with both intestinal and diffuse type of carcinoma is *Helicobacter pylori*, recognized as a definite carcinogen for gastric cancer. The complex interrelation between *Helicobacter pylori* strain, inflammation and host characteristics may directly promote diffuse type gastric cancer or induce a cascade of morphological events, i.e. atrophy, intestinal metaplasia and dysplasia, leading to intestinal type gastric cancer. The sequential process of carcinogenesis involves mutations in oncogenes, tumour suppressor genes and cell cycle and mismatch repair genes.

KEY WORDS *Helicobacter pylori*, carcinogenesis, intestinal type gastric carcinoma, diffuse type gastric carcinoma, molecular events.

Review

Even until recently, gastric cancer was considered the second most common cancer worldwide, now it becomes the fourth as frequency, behind lung, breast, and colon and rectum cancers. This malignity is also the second most common cause of death from cancer. Almost two-thirds of the cases occur in developing countries and the geographical distribution of stomach cancer is characterized by wide international variations; high-risk areas include East Asia (China, Japan), Eastern Europe, and parts of Central and South America; incidence rates are low in Southern Asia, North and East Africa, North America, and Australia and New Zealand (18). Over the last several decades there has been a steady decline in the risk of gastric cancer incidence and mortality in most countries that may be related to improvements in preservation and storage of foods and also reflect the changes in the prevalence of *H. pylori* infection (18).

The pathogenesis of gastric cancer represents a classic example of environment-gene interaction and an important epidemiological aspect in gastric cancer was the recognition of the association with *Helicobacter pylori* infection, some independent studies reporting a significantly increased risk in subjects that have had *Helicobacter pylori* infection 10 or more years before the cancer diagnosis (20). Consequently, over the last few years, it has become apparent that the most important single factor responsible for the development of gastric cancer is *Helicobacter pylori* infection that affects more than 50% of the

world population and the risk for gastric cancer is influenced primarily by the presence of *Helicobacter pylori* classified as a group I carcinogen by the World Health Organization's International Agency for Research on Cancer has (IARC) (9).

Helicobacter pylori infection increases the risk for gastric cancer depend primarily on the age *Helicobacter pylori* infection and involves microbial virulence factors as well as the host response to the bacteria.

In gastric carcinogenesis, *Helicobacter pylori* may act either directly or inducing an inflammatory response. The presence of *Helicobacter pylori* in gastric mucosa is associated with synthesis of different substances such as ammonia, phospholipases, and cytotoxins, which are thought to cause epithelial damage leading to a persistent state of proliferation and regeneration with, increased the risk of malignant alterations of the gastric stem cells at the neck region of the gastric glands (1). On the other side, the injury of the gastric mucosa is increased by the action of free radicals in the form of NO and reactive oxygen metabolites released from neutrophils in the inflammatory process, as part as the host's immune response toward infection, and that are responsible for AND damage.

The major *Helicobacter pylori* virulence factors are the Cag (cytotoxin-associated antigen) pathogenicity island (PAI), the CagA protein, the vacuolating toxin VacA, the blood group antigen binding adhesin (BabA) and possibly the duodenal ulcer-producing gene (dupA); the more virulent

cagA- and vacA-positive type 1 strain induces a more pronounced inflammatory response with an increased risk for gastric cancer, particularly of intestinal type (19).

The importance of host genetic factors was indicated by the association of interleukin-1 gene polymorphisms with an increased risk of developing gastric atrophy in the presence of *Helicobacter pylori*. IL-1 β , with a proinflammatory role and a powerful inhibition of acid secretion in gastric mucosa, is up regulated by the bacterial infection and became relevant to the pathogenesis of *Helicobacter pylori*-induced inflammation and the subsequent neoplastic process (5). When these polymorphisms are combined with bacterial virulence factors, such as CagA, vacA s1 and vacA m1 positivity, the risk of developing the disease is greatly enhanced (6). Moreover, the mucosal infection with *Helicobacter pylori* is associated with increased expression of apoptosis-regulating proteins as Bax and Bcl-2 suggesting the loss of control of these apoptosis-regulating genes that may lead to gastric carcinogenesis; these genes are also more markedly expressed with cagA-positive *Helicobacter pylori* strains (27).

The Lauren's classification recognizes two major histological types of gastric carcinoma (intestinal and diffuse) with distinct pathogenesis and particular genetic alterations (12). Human gastric carcinogenesis occurs in a multistage process defined by distinct histological and physiopathological phases and originating in epithelial stem cells by accumulation of molecular alterations involving either defect in tumor suppressor genes or defect in DNA mismatch repair genes that follow different genetic pathways for each of intestinal and diffuse type of gastric carcinomas the intestinal type is often preceded by sequential precancerous changes, including atrophic gastritis, intestinal metaplasia, and either dysplasia or adenoma, while the diffuse type of gastric carcinoma tends to arise de novo and is infrequently associated with dysplasia or adenoma, even it is also related with *Helicobacter pylori* infection (23, 26).

In gastric carcinoma of the intestinal type, the Correa's biological model of gastric carcinogenesis designate a series of sequential phases starting from chronic gastritis and progressing through chronic atrophic gastritis, intestinal metaplasia and dysplasia to carcinoma (3). This sequence is usually triggered by *Helicobacter pylori* infection and influenced by a variety of genetic and environmental factors that may act synergistically.

The development of the intestinal type of gastric cancer begins with the induction of a chronic inflammation as response to *Helicobacter pylori* infection that leads to alterations of the epithelial cell cycle, particularly to increased rates of apoptosis and cell proliferation responsible for the multifocal atrophy that characterizes the type of gastritis associated with an increased risk of cancer. If gastritis persists, the subsequent gastric atrophy is followed by intestinal metaplasia, which may lead to dysplasia that can arise in either native gastric or "intestinalized" gastric epithelium. The extent and topography of *Helicobacter* gastritis is related with the risk of subsequent carcinoma, tumor development being associated with much more severe gastritis in the corpus of the stomach in contrast to the antral-predominating gastritis in duodenal ulcer setting (15). It was also described a genetic susceptibility for gastritis of the gastric cancer phenotype related with the number of acid-producing parietal cells in stomach mucosa as in the individuals with an "inherited" comparatively low number of parietal cells, *Helicobacter pylori* gastritis might manifest predominantly in the corpus with an associated increased individual's gastric cancer risk. Interestingly, corpus-predominating "gastric cancer phenotype" of *Helicobacter pylori* gastritis also occurs more often in relatives of gastric carcinoma patients (16).

Long-standing *Helicobacter pylori*-induced gastric inflammation often leads to atrophic gastritis that is considered the first important step in gastric cancer histogenesis (4). The atrophy of gastric mucosa, particularly when it affects a large part of the gastric body, is associated with acid hyposecretion and low gastric acidity, allowing the colonization with other bacteria that may promote the formation of other carcinogenic factors, i.e. N-nitroso compounds, with subsequent cellular genome injury (DNA methylation) (13).

Since *Helicobacter pylori* is proven to be associated with the progressive development of metaplastic changes, the chronic atrophic gastritis is often associated with intestinal metaplasia that has been classified according to Jass and Filipe as complete or type I, or incomplete which comprises types II and III (10). It has been suggested that the risk of gastric carcinomas is related to the type of intestinal metaplasia and with its gastric distribution as the gastric cancer is more frequent in association with type III intestinal metaplasia rather than type I and with intestinal metaplasia involving the lesser curvature, from cardia to the pylorus, or the entire stomach, rather than with focal or antral predominant metaplasia (2).

Progression of intestinal metaplasia to gastric carcinoma may involve certain molecular alteration and the non-neoplastic adaptable changes in gastric cell phenotype that characterize intestinal metaplasia reflect the consequence of a modified microenvironment under *Helicobacter* infection and it seems to involve cytokines from chronic inflammatory cells (26). This process is either a result of genetic mutations in stem cells or epigenetic events that produce divergent differentiation in progenitor cells; the genetic permanent mutations, generally found in type III intestinal metaplasia, are similar to those found in gastric dysplasia (25). *Helicobacter pylori*-associated intestinal metaplasia, particularly the type III one, and the intestinal metaplastic areas adjacent to gastric carcinomas associate accumulation of p53 mutations and alterations of cell cycle regulators as overexpression of COX-2 and cyclin D2 and decreased p27 expression (22).

The directly precancerous step in the sequence of morphological changes leading to gastric carcinogenesis is dysplasia that usually develops in the intestinal metaplastic background [4]. The gastric dysplasia, has been recently defined as 'non-invasive neoplasia' in a five-tier classification system: negative for neoplasia/dysplasia; indefinite for neoplasia/dysplasia; non-invasive neoplasia, low grade; non-invasive neoplasia, high grade; invasive neoplasia (21). From a molecular viewpoint, dysplastic cells have an increased amount of DNA, partly due to the increased number of proliferating cells and high-grade dysplasia contains a mixture of polyploidy and aneuploidy cells (14). Gastric dysplastic mucosa over expresses several markers as APC/MCC (adenomatous polyposis coli /mutated in colon cancer) loss of heterozygosity, carcinoembryonic antigen, tumor suppressor gene p53 and the apoptosis inhibitor bcl-2 gene that are also found in carcinomas (17).

Regarding the diffuse-type of gastric carcinogenesis, since atrophic changes are not severe in this variant it was previously considered to have little relation to *Helicobacter pylori* infection (23). However, epidemiological and histopathological studies have shown that the development of diffuse-type cancer is closely related to *Helicobacter pylori* infection, in some reports, diffuse-type gastric cancer being associated with moderate atrophic changes and pangastritis (11). Considering these observations, in diffuse carcinomas, the gastric neoplasia develops in a mucosa following chronic inflammation without passing through the intermediate steps of atrophic gastritis or intestinal

metaplasia. Is the severity of the mucosal inflammation and host characteristic that may directly induce mutagenetic events ultimately leading to cancer (7). Even the onset of these molecular alterations is strongly associated with *Helicobacter pylori* infection, the genetic alterations detected in diffuse type of gastric cancer differ substantially from those found in the intestinal type, i.e. MSI-H phenotype (high-frequency microsatellite instability), implicated in the repair of spontaneous and toxic DNA damage; SC-1 antigen (specific cell-surface receptor), an apoptotic receptor; E-cadherin (adhesion molecule) mutation and the growth factors c-met and k-sam (8, 25).

Conclusions

Gastric carcinomas involve *Helicobacter pylori* as primary carcinogen and result from a complex interaction between bacterial, environmental and host-genetic factors involving certain molecular mechanisms. The comparison between the genetic expression profiles in diffuse-type and intestinal-type of gastric cancers identified distinct molecular alteration particularly distinctive for each histological type. The intestinal-type cancer is characterized by enhancement of cell growth whereas the diffuse-type cancer exhibit altered expression of genes related to cell-matrix interaction and extracellular-matrix components. Even if intestinal and diffuse type gastric carcinomas evolve from a different genetic pathways, they depend of the same triggering factor i.e *Helicobacter pylori*-associated inflammatory response that initiate a cascade of sequential events (mucosal atrophy, intestinal metaplasia and dysplasia) progressing to intestinal type of carcinoma or directly induce the diffuse type of cancer. Once the pathway is initiated, the progression to cancer may develop independent of *Helicobacter pylori* presence, the molecular alterations underlying gastric carcinogenesis being either genetic (irreversible changes in the DNA sequence) or epigenetic (DNA methylation, potentially reversible by eliminating the triggering agents). The early eradication of *Helicobacter pylori*, before development of permanent genetic mutations may prevents the risk of gastric cancer.

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