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THE MOLECULAR AND CLINICAL INTERPLAY BETWEEN HELICOBACTER PYLORI INFECTION AND GASTRIC CARCINOGENESIS: A COMPREHENSIVE REVIEW

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ABSTRACT Gastric cancer is a complex ailment characterized by numerous contributing factors, and it represents a substantial contributor to mortality rates. The risk factors associated with this illness involve a combination of environmental factors and factors that influence the interaction between the host and pathogens. The aforementioned elements exhibit complex interplay, hence augmenting the progression of stomach cancer. Gastric adenocarcinomas can be classified into two separate forms: intestinal and diffuse. There exists a hypothesis suggesting a potential causal relationship between the infection of Helicobacter pylori (H. pylori) and the development of chronic active gastritis, which in turn could contribute to the subsequent creation of intestinal-type adenocarcinoma The activation of oncogenic pathways by CagA and peptidoglycan, which are delivered into the gastric epithelial cells during H. pylori infection, is considered a significant contributing factor to tumor growth. The application of antibiotics in the eradication of H. pylori has the potential to reduce the incidence of precancerous lesions. However, this impact is predominantly found in the early stages of stomach carcinogenesis. The acquisition of this knowledge has the potential to significantly augment the efficacy of preventative strategies and therapeutic therapies for stomach cancer. The present review offers a complete examination of the existing literature about gastric cancers, with specific emphasis on the influence of Helicobacter pylori infection. The advancement of cancer is aided by the interactions that take place between the immune system of the host and microorganisms.

KEYWORDS : Helicobater pylori, gastritis, peptic ulcer, Intestinal metaplasia, gastric cancer

INTRODUCTION:

Gastric cancer (GC) is a multifactorial disease in which both genetic and environmental factors are involved. According to the statistics, GC is the fourth cause of cancer death worldwide, with a median overall survival of ≤12 months for advanced stage(1). It is rare in the younger population, where less than 10% of patients suffer from GC before 45 years of age (2–4). It is highly heterogeneous disease with different molecular and genetic alterations. Gastric cancer (GC) is a frequently diagnosed malignancy and it is a leading cause of cancer-related mortality in affluent nations. The objective of this review is to examine the dissemination of gastric cancer (GC) and its primary risk factors, with particular attention to the influence of Helicobacter pylori infection. H. pylori is well acknowledged to have a significant role in the chronic inflammation associated with duodenal ulcers and gastric illnesses. Consequently, it is imperative to comprehend the mechanisms by which H. pylori facilitates the transition from acute mucosal inflammation to gastric cancer (GC).

The Impact of Helicobacter pylori infection on the Stomach:

Helicobacter pylori (H. pylori) is well recognized as the prevailing infection worldwide, with significant implications as the etiological agent responsible for gastric cancers (GCs) (5). The infection caused by Helicobacter pylori (H.pylori) significantly increases the likelihood of developing stomach cancer, nearly doubling the overall risk. Gastric cancer (GC) progresses via a series of distinct and identifiable stages: inflammation, atrophy, intestinal metaplasia, dysplasia, and carcinogenesis. These stages are strongly linked to many factors such as environmental influences, dietary patterns, and genetic alterations (6). The recognition patterns of gastric cancer encompass various genetic alterations involving cell cycle regulators, factors governing apoptosis, microsatellite instability, multidrug resistance proteins, factors influencing cell membrane properties, module of HER2 expression, and agents influencing the progression of gastric cancer and peritoneal metastasis (7).

The cells present in the gastric mucosa are responsible for the production of hydrochloric acid, which facilitates the process of food digestion within the stomach under conditions of low pH. However, it is important to note that these cells do not possess complete resistance to acidity. Consequently, in typical circumstances, a delicate coating of defensive mucus is present. Nonsteroidal anti-inflammatory medicines (NSAIDs), such as acetylsalicylic acid, have been found to cause damage to the gastric mucosa and contribute to the formation of ulcers. This is mostly attributed to their inhibitory effect on prostaglandin synthesis, which subsequently hampers the activation of mucus production in the stomach(8). Helicobacter pylori has the ability to adjust and acclimate to the specific environmental conditions that exist within the stomach, particularly in the pylorus region. The avoidance of regions characterized by significantly low pH levels effectively directs the illumination within the stomach away from its inner linings. The migration occurs towards the epithelium of the mucous membrane, where it subsequently infiltrates the mucus layer that envelops the cell. Individuals with higher levels of hydrochloric acid secretion are more prone to bacterial colonization in the pylorus, particularly at the anatomical junction where the stomach transitions into the duodenum. By employing this method, the region of the stomach that exhibits a notably low pH is circumvented. The colonization of the entire stomach by H. pylori occurs when there is a decrease in hydrochloric acid output (9).

The locomotion of bacteria is an active process that is facilitated by their distinctive morphology. Subsequently, Helicobacter pylori exhibits adherence to epithelial cells and is capable of penetrating them. The immune system's response to H. pylori bacteria plays a crucial role in defining the resulting repercussions of the illness. Helicobacter pylori is able to endure acidic environments through the secretion of urease, an enzyme that facilitates the breakdown of urea, resulting in the production of ammonia. This process effectively raises the pH of its surrounding environment. Ammonia is recognized as a harmful by-product resulting from the metabolic activities of Helicobacter pylori(10).

Helicobacter pylori infection-induced oxidative damage

One crucial determinant in the sequence of events leading to the development of inflammation-to-carcinoma is the occurrence of oxidative DNA damage caused by H. pylori infection. This damage is likely attributed to the infiltration of neutrophils and the direct impact of H. pylori. The production of reactive oxygen species (ROS) in the gastric epithelium that is infected with Helicobacter pylori is linked to the presence of cagPAI and contributes to the induction of oxidative stress in gastric epithelial cells(11). The correlation between H. pylori infection and increased levels of polyamines, specifically spermine, is widely recognized. This increase has been observed to coincide with the activation of spermine oxidase(12).The enzymatic activity of spermine oxidase on spermine results in the generation of increased quantities of hydrogen peroxide, a potent oxidizing agent that also contributes to the formation of free radicals, including the hydroxyl radical. In addition, Helicobacter pylori also induces the activation of macrophages, leading to a notable increase in the expression of spermine oxidase. This enzymatic overexpression contributes to the occurrence of oxidative stress and subsequent damage to the gastric epithelial cells(13). Additionally, the infection of gastric epithelium results in modified polyamine metabolism and the upregulation of the arginase enzyme, which subsequently leads to a reduction in nitric oxide (NO) production and an increase in the synthesis of spermine and hydrogen peroxide.

Helicobacter pylori and its role in carcinogenesis

The infection of gastric epithelium by H. pylori results in the progression of intestinal-type adenocarcinoma, wherein the initial occurrence involves the transformation from normal mucosa to chronic superficial gastritis. Subsequently, the emergence of atrophic gastritis is succeeded by the onset of intestinal metaplasia, ultimately culminating in the advancement of dysplasia and the genesis of adenocarcinoma(14). According to a study, the male gender exhibits a twofold higher susceptibility to the intestinal type of gastric adenocarcinoma compared to females(15). The outcomes are influenced by the location of infection and the development of gastritis. Hence, it can be deduced that corpus-predominant gastritis is correlated with a heightened probability of developing gastric cancer, possibly as a result of diminished acid output. On the other hand, the infection of the gastric antrum, which induces the formation of acid, renders individuals more vulnerable to duodenal ulceration. However, it paradoxically diminishes the likelihood of developing gastric cancer(16).

The pathogenesis of gastric cancer is significantly impacted by the genetic variability of H. pylori, which leads to the presence of many virulence factors that play a crucial role in this process. The presence of CagA, a protein encoded by the DNA insertion element known as cag pathogenicity island (cagPAI), has been identified as a significant factor in the development of carcinogenesis. Consequently, it has been observed that only Helicobacter pylori strains containing the cagPAI element are associated with an increased risk of atrophic gastritis and gastric cancer, despite the fact that all strains of this bacterium have the potential to cause gastritis.The CagA protein, with a molecular weight ranging from 120 to 140 kilodaltons, undergoes translocation into host cells subsequent to bacterial adhesion to the cell. CagA undergoes phosphorylation by Abl and Src kinases within the intracellular environment, specifically on tyrosine residues located at four discrete glutamate-proline-isoleucine-tyrosine-alanine (EPIYA) motifs situated at the protein's C-terminal region. This phosphorylation event induces various morphological alterations in the host cell, such as enhanced cell migration. The quantity and phosphorylation state of these EPIYA motifs serves as a decisive factor and indicator of susceptibility to gastric cancer(17). The activation of tyrosine phosphatase (SHP-2) in the host cell is initiated by Tyr-phospho-CagA, resulting in the prolonged activation of ERK1/2, Crk adaptor, and C-terminal Src kinase(18). The phenomenon of cell elongation is observed as a result of the interaction between phosphor-CagA and SHP. The detrimental impacts of CagA are evident even when it is not phosphorylated, as it induces aberrant activation of Î2-catenin, disturbance of apical-junctional complexes, and impairment of cellular polarity(19). In addition, CagA that is not phosphorylated specifically interacts with many cellular components, including E-cadherin, the c-Met receptor for hepatocyte growth factor, phospholipase C-γ, the adaptor protein Grb2, and other molecules. These interactions subsequently result in the activation of proinflammatory and mitogenic signaling pathways, as well as the rupture of cell-cell junctions and the loss of cell polarity.

In addition to CagA, Helicobacter pylori peptidoglycan has the ability to be transported into host cells. Once inside, peptidoglycan interacts with NodI, resulting in the activation of the NF-κB dependent pro-inflammatory pathway. This activation leads to the release of interleukin (IL)-8, a cytokine known for its inflammatory properties. The activation of the PI3K-Akt pathway by peptidoglycan has been demonstrated to induce cell proliferation, migration, and inhibit apoptosis (20).

Additional virulence factors found in Helicobacter pylori include VacA and outer membrane proteins, which have been linked to the development of ulcers and stomach cancer (21). Vacuolating cytotoxin A (VacA) is known to elicit cellular vacuolation and apoptosis, hence facilitating tissue injury and inflammation.

The predominant categorization system utilized for stomach cancer is the Lauren classification. The text presents a distinction between two types of gastric cancer, namely intestinal and diffuse. These types can be differentiated based on several distinguishing factors such as morphology, genetics, clinical characteristics, progression pattern, and epidemiology (22). Diffuse-type gastric cancer (GC) is characterized by the presence of individual cells that lack cohesive properties and do not form glandular structures. Gastric cancer of the intestinal type is characterized by the presence of glandular or tubular components exhibiting varying levels of differentiation(23). Although there has been a global decline in the occurrence of gastric cancer (GC), it is noteworthy that the incidence of GC characterized by signet-ring cell histology is on the rise. Historically, gastric carcinoma characterized by the presence of signet-ring cells was categorized as the "diffuse type" based on Lauren's classification(22). Signet-ring cell carcinoma is characterized as a poorly cohesive carcinoma primarily consisting of tumor cells with significant cytoplasmic mucin and a crescent-shaped nucleus that is eccentrically positioned (24). It is imperative to comprehend that the categorization of stomach cancers as "undifferentiated" or "diffuse" does not universally imply the presence of signet-ring cell tumors.

Gastric cancer is a complex disease with multiple contributing variables, among which Helicobacter pylori (H. pylori) infection is recognized as a risk factor, although it is not the sole determinant. The presence of H. pylori infection significantly elevates the likelihood of getting gastric cancer by a factor of around six (23, 25). In 1994, the classification of H. pylori as a class I carcinogen was carried out by the World Health Organization (WHO) (23,26). Helicobacter pylori, alternatively referred to as Campylobacter pylori, was first identified by Australian researchers in 1982. This bacteria was found in the mucous membrane of the human digestive tract(27). The nomenclature of H. pylori incorporates the term "pylori" due to its predominant detection in the distal region of the stomach, known as the pylorus. The research revealed that gastric acid does not inflict harm on H. pylori and, in fact, appears to be crucial for its proliferation. Subsequent studies

demonstrated that H. pylori has the ability to infect many tissues, such as the liver and the eye (28,29).

Subsequent investigations revealed a correlation between the presence of Helicobacter pylori in the upper gastrointestinal tract and the occurrence of gastric and duodenal ulcers. Nevertheless, it is important to note that the presence of a bacterial infection does not necessarily imply the occurrence of peptic ulcer disease. Gastric cancer is observed in only a minority of those who have been infected. The prevalence of H. pylori infection has been seen to vary, with rates ranging from around 60% in the general population to approximately 84% in those diagnosed with stomach cancer (30). There exist additional crucial cofactors that exert an influence on risk, potentially elucidating the observed variations in morbidity across different racial and gender groups. Approximately 50% of the global population, with a higher prevalence observed in poorer nations, is afflicted with H. pylori infection. In the context of peptic ulceration affecting the stomach and duodenum, it has been shown that a notable proportion, specifically ranging from 5% to 10%, of the adult population experiences this affliction. Despite the absence of clinical signs in the majority of individuals with H. pylori infection, prolonged infection has the potential to cause inflammation of the gastric epithelium. It has been observed that around 10% of infected patients develop peptic ulcers, while gastric adenocarcinoma develops in 1-3% of subjects (31). Thus, it can be concluded that Helicobacter pylori is not solely responsible for the development of all gastric and duodenal ulcers, and its presence alone cannot fully elucidate the underlying mechanisms of gastric cancer(32).

Influence of Environmental Factors on H. Pylori Infection:

The development of gastric adenocarcinoma is significantly impacted by the consumption of dietary salt, as higher levels of salt intake have been found to exacerbate the formation and growth of tumors . Epidemiological studies have provided evidence suggesting a positive correlation between elevated salt consumption and the higher prevalence of H. pylori infection (33), as well as an increased occurrence of gastric adenocarcinoma in those who are infected (34). The results of experimental research have demonstrated that there is a synergistic relationship between a diet rich in salt and H. pylori infection in the development of premalignant lesions or gastric cancer (35). This impact is likely due to an increase in the production of inflammatory cytokines, including IL-1, IL-6, and TNF-α (36). Nevertheless, the specific molecular mechanisms responsible for this synergistic impact on the development of cancer remain unidentified. There is a suggestion in the literature that elevated levels of salt may lead to an increase in the production of CagA, a possible carcinogen found in H. pylori (37).

Besides sodium chloride, there are other factors that exert an influence on the development of gastric cancer linked with H. pylori infection. These factors include helminth infections and dietary consumption of antioxidants, both of which appear to have a detrimental impact on the ability of H. pylori to initiate gastritis and subsequently promote the development of cancer. In contrast, the act of smoking cigarettes has the ability to increase the likelihood of carcinogenesis caused by H. pylori infection (38).

Management and Eradication Challenges:

Antibiotic Resistance:

The eradication of H. pylori is of utmost importance in order to mitigate the risk of stomach cancer. The initial therapeutic approach often entails the concurrent use of proton pump inhibitors (PPIs) and antibiotics(39). Nevertheless, the issue of antibiotic resistance is becoming increasingly worrisome, underscoring the necessity for alternate therapeutic approaches and preventive measures(40).

Reinfection:

In some endemic locations, the possibility of reinfection exists even following successful eradication(41).

Prospects for the Future:

The expanding understanding of the pathophysiology of stomach cancer associated with Helicobacter pylori has instilled optimism for the development of more precise therapeutic interventions. The investigation of probiotics, bacteriophages, and vaccinations in the management and prevention of H. pylori infections is currently a subject of ongoing scholarly inquiry.

Concluding Remarks:

The correlation between Helicobacter pylori and stomach cancer highlights the significance of comprehending the interactions between microorganisms and the human body. The implementation of early detection, prompt treatment, and preventative measures has the potential to substantially alleviate the worldwide impact of stomach cancer.

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