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Abstract

Gastric cancer is a major public health concern due to the many deaths it is associated with. H. pylori is present in almost all gastric cancer patients; thus, it is fundamental to understand how H. pylori is implicated in the etiology of gastric cancer. The research in this paper is primarily based on studies acquired from Touro College Online Libraries. The bacteria have the means to survive the harsh environment of the stomach by creating a safe microenvironment and propelling themselves toward safer territory. If the bacteria attach to host cells, H. pylori injects cytotoxin-associated protein A (CagA) and vacuolating cytotoxin A (VacA) into their host, inducing inflammation and disrupting cell functions. H. pylori continues to survive at the surface epithelia through various functions and causes damage to epithelial cells. Following gastritis, ulceration or gastric cancer may develop. Mechanisms of the proliferation of cells are abundant but stem from the destruction of cells due to inflammation. The prognosis of gastric cancer is poor due to the advanced stage of cancer at the time of detection. Surgical removal of the tumor, although sometimes employed, is not always recommended or successful. Since a large majority of individuals are infected with non-pathogenic strains of H. pylori, treatment isn't always suggested. Moreover, some research suggests that there are benefits to being infected with H. pylori.

Introduction

It was long believed that duodenal and gastric ulcers were caused by stress and lifestyle. In the 1980s, Warren and Marshall (reported in Huang 2016) the association of a spiral-shaped, Gram-negative bacterium with gastric and duodenal ulcer biopsies. They published these findings but were not believed by many because of the belief that bacteria cannot live in the stomach due to its harsh conditions of a low pH. Failure to induce animals with H. pylori prevented animal experimentation. Dr. Marshall infected himself with the bacteria and developed pain and inflammation. Endoscopy revealed the same spiral shape bacteria (Huang, 2016). This supported his and Warren's hypothesis. Antibiotic treatment trials prevented the relapse of ulcers. They were awarded the Nobel Prize in 2005 for their link of Helicobacter pylori to gastritis and peptic ulcer disease ("The Nobel Prize in Physiology or Medicine 2005"). H. pylori infects about half of the world's population, although it is not equally distributed in each geographical location. It is not fully understood how it is contracted but is assumed to come from contaminated drinking water or through the fecal-oral route. Infection generally occurs during childhood; if not treated with antibiotics, it can last a lifetime (Perkins et al., 2013).

Gastric cancer is one of the leading causes of death worldwide. Although a large percentage of individuals in every population are infected with H. pylori, many are asymptomatic (Min Ho Lee et al., 2019). Less than one percent of those infected with H. pylori will develop gastric cancer; however, those with gastric cancer present with H. pylori in most cases (Min Ho Lee et al., 2019; Xie et al., 2008). Many studies show that H. pylori infection is associated with a host of stomach problems, including gastric adenocarcinoma, peptic ulcers, gastric inflammation, and chronic gastritis (Min Ho Lee et al., 2019). Because of this, the WHO has classified H. pylori as a class I carcinogen (Min Ho Lee et al., 2019).

This paper is intended to be a critical review of research projects that have been conducted to better define the mechanisms by which H. pylori leads to gastric cancer. A better understanding of the connection would provide specific methods of prevention as well as treatments to target the progression of the bacterial infection. Just as Dr. Warren and Marshall successfully proved that H. pylori is linked to gastritis and peptic ulcer disease, perhaps it can be determined how H. pylori is implicated in the etiology of gastric cancer.

Methods

Data for this paper was compiled from the databases of Touro College Online Libraries, primarily ProQuest, and was supplemented by additional websites. Keywords used include H. pylori, gastric cancer, CagA, and gastroesophageal reflux disease (GERD).

Discussion

Mechanisms of Infection

H. pylori is a bacterium only found in the digestive tract (Fung, 2018). Although it lives in the stomach, H. pylori is a neutrophile with optimal growth conditions at a slightly acidic pH (Liao, 2020). Since the pH in the stomach is about two, the bacteria have two ways of surviving the harsh environment. First, H. pylori contains the protein urease, which breaks down urea into ammonia and carbon dioxide. The urease breath test contains carbon thirteen marked urea, which gets converted to carbon thirteen marked carbon dioxide in H. pylori positive patients. Ammonia allows the bacteria to neutralize the acid, creating a microenvironment with a higher pH. Second, by use of their flagella, the bacteria swim away from the low pH of the stomach to the mucosa layer, which has a higher pH. (Huang, 2016). The TlpB protein detects low levels of pH (Liao, 2020). Once in the mucus covering of the epithelial lining, the bacteria can circulate freely in their microenvironment. Some strains of the bacteria are equipped with fimbriae, allowing them to attach to the surface of the epithelial cells that make up the glands that secrete the mucus. The bacteria then divide, creating

microcolonies at the junctional complexes (Huang, 2016). This is where the problem starts.

Virulence factors of H. pylori

H. pylori can live in the mucus layer without causing symptoms. This is the large subset of those infected by H. pylori but not affected by it. They present with moderate gastritis and mild changes in acid secretion (Fung, 2018). Microcolonies that are attached to the surface of the epithelial cells have been found to cause more prominent inflammation, leading to complications (Dorer et al., 2010). It has been reported that the most well-known virulence factors of H. pylori are the cytotoxin-associated protein A (CagA) and vacuolating cytotoxin A (VacA) proteins present in pathogenic strains of H. pylori (Saha et al., 2010). These bacterial proteins are secreted into the host after contact is made via type IV and type V secretion systems (T4SS, T5SS). Once injected, CagA distorts epithelial junctions and cell morphology, promotes inflammation, and, more importantly, takes control over signaling pathways. Both CagA and VacA migrate to the periplasm of the bacterial cell through Sec-related proteins, which operate with ATP.

VacA generates vacuole production and eventually leads to apoptosis. It does this by changing the mitochondrial membrane potential in the host cell and causing the mitochondria to release cytochrome c, which starts the breakdown of cells (Min Ho Lee et al., 2019). VacA also prevents the actin filaments from adhering to the parietal cells at the lumen (Saha et al., 2010). The bacteria remain attached to the surface of the epithelial cells and inject these proteins. This causes chronic inflammation in the gastric mucosa and the presence of many pro-inflammatory cytokines such as nuclear factor-kB (NF-kB) and interleukin 8 (IL8). NF-kB activates the specific genes that control inflammation in the gastric mucosal layer, one of which is IL8 (Min Ho Lee et al., 2019). IL8 is associated with tumor growth and secondary tumors. Additionally, IL8 plays a role in angiogenesis, the formation of new blood vessels (Kang et al., 2013). Studies have shown that those with increased levels of IL8 in their blood are at an increased risk for gastric cancer (Epplein et al., 2013). IL8 inhibits the H, K ATPase on parietal cells from functioning, raising the pH (Saha et al., 2010).

Essentially, by releasing CagA and VacA, H. pylori increases inflammation. Thus, it is important to understand how some of the strains of H. pylori adhere to the surface.

Survival of H. pylori at the surface epithelia

Anemia is a less common symptom of H. pylori. H. pylori thrives in iron-deficient hosts. CagA acquires iron from the host cell by altering cell activity. Catalase, one of the proteins of H. pylori, breaks down hydrogen peroxide, which is produced by inflammation, into water and hydrogen gas, which are less toxic substances. This is thought to aid in the survival of H. pylori (Fung, 2018).

Some strains of the bacteria make their way through the pits and down into the base of the gastric glands, where they colonize epithelial cells. Deep in the glands are stem and epithelial precursor cells. It is here where the bacteria affect proliferation, in addition to inflammation and hyperplasia leading to gastric cancer (Fung, 2018).

Ulceration vs. Gastric Cancer

According to many research studies, those who develop ulcers do not develop gastric cancer. The reason for this "protection" is largely unknown but thought to be associated with specific sites of colonization and levels of hypochlorhydria. Ulcers develop via changes in cell structure and inflammation, leading to apoptosis of epithelial cells. CagA is responsible for inflammation. Chronic inflammation leads to peptic ulcers in ten to fifteen percent of those infected with H. pylori. Persistent inflammation in the antrum (Fig. 1) results in increased acid production in the corpus, and this causes damage to the duodenum, which responds with gastric metaplasia. Some argue that H. pylori can colonize the modified duodenum as opposed to regular duodenal epithelial cells, which H. pylori does not infect. Ulcers form in the corpus and antrum, i.e., gastric ulcers, as well as in the duodenum.

Treatment of ulcers is the same as the treatment of H. pylori, whereas treatment for gastric cancer is not particularly effective since detection most often occurs at advanced stages (Fung, 2018). In light of these findings, H. pylori infection of the antral mucosa is thought to be associated with gastric and peptic ulcers, while infection of the oxyntic mucosa, mucus of the fundus and corpus (Fig. 1), is associated with gastric cancer (Waldum et al., 2015).

Evidence for a Causative Role in Gastric Cancer

Most patients that have gastric cancer are positive for H. pylori. Although rare, some gastric cancer patients do not have H. pylori, and these patients generally have less malignant tumors (Tanaka et al., 2022). H. pylori positive gastric cancer patients treated for the infection were compared to a control group who did not receive antibiotics. The assessment was conducted to take note of additional tumor development. In the group that was treated, fewer patients developed additional tumors. Moreover, no significant side effects were associated with the eradication of H. pylori (Kikuchi et al., 2008).

Proliferation of Cells

Inflammation serves to promote cancer development and progression due to its fertile and pro-growth environment (Epplein et al., 2013). Different theories exist as to how gastric cancer develops from the inflammation caused by H. pylori.

CagA activates NF-kB, although it is arguable how significant CagA is to the activation. NF-kB regulates the expression of the enzyme phospholipase D1 (PLD1), which is upregulated in those with gastric cancer as well as other cancers. PLD1 breaks down phospholipids and is associated with cell growth (Kang et al., 2013).

CagA causes upregulation of cyclo-oxygenase-2 (COX-2), which is an enzyme responsible for the synthesis of prostaglandins (Fig. 2). COX-2 is angiogenic, which provides nutrients to cancerous cells. E-cadherin is responsible for cell adhesion and is produced from epithelial cells. COX-2 frees E-cadherin from the cell membranes, promoting the spread of tumors. When inflammation is present, E-cadherin is liberated, and soluble E-cadherin is found in elevated levels in the blood, a risk factor for cancer. The loss of cell-cell adhesions is thought to aid H. pylori in progressing further into the lamina propria, where it can continue to cause damage. One study suggests that the presence of Cox-2 prevents apoptosis of malignant tissue (Anwar et al., 2012).

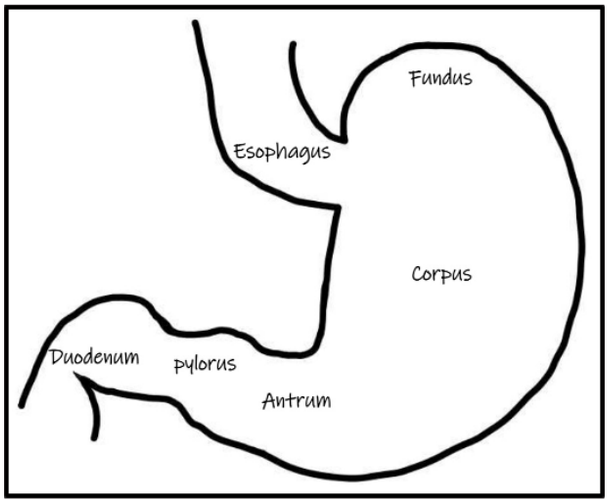

Fig. 1 Diagram depicting regions of the stomach

Once in the host, CagA becomes phosphorylated and causes abnormal epithelial cell proliferation (Saha et al., 2010). Non-atrophic gastritis begins with the presence of an inflammatory response of white blood cells in the gastric mucosa of the corpus (Fig. 1). Gastric glands are destroyed due to chronic inflammation causing atrophic gastritis. Due to the loss of the parietal cells, the pH of the stomach rises, which is called hypochlorhydria, which leads to hypergastrinemia, excess gastrin production (Fig. 2). Hypochlorhydria triggers stem cells and precursor cells to proliferate. During this time, cells may mutate, leading to adenocarcinoma (Fung, 2018). Additionally, it is suggested that since the function of acid in the stomach is to kill ingested organisms when the acidity is lessened, other microbes may be able to survive, leading to cancer (Waldum et al., 2015).

Hypergastrinemia also stimulates the chief cells to produce pepsinogen and the proliferation of enterochromaffin-like (ECL) cells (Fig. 2). Because of this, H. pylori positive patients have high levels of pepsin, the active form of pepsinogen, as well as gastrin, in their blood (Horiuchi et al., 2016; Waldum et al., 2015). A positive pepsinogen test is a risk factor for atrophic gastritis (Horiuchi et al., 2016). The use of netazepide, a gastrin antagonist, was found to reduce atrophy and inflammation in the oxyntic mucosa. ECL cells produce histamine and send it to neighboring parietal cells to help with the secretion of acid. One study demonstrated that loxtidine, a histamine-2 blocker, was found to protect against neoplasia, indicating the possible mutated histamine from ECL cells. Additionally,

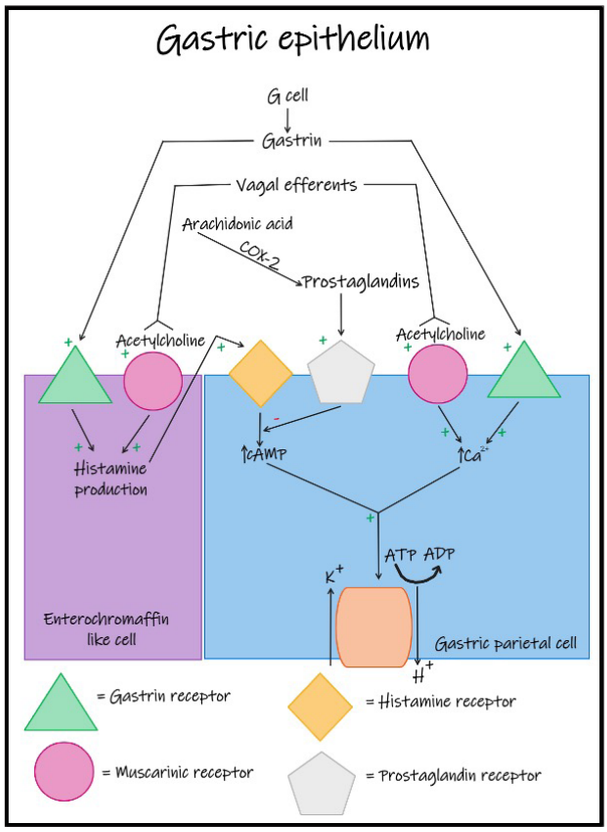

Fig. 2 Diagram depicting gastric epithelial cell processes

if unresolved, chronic hypergastrinemia leads to tumor formation in ECL cells (Waldum et al., 2015).

Treatment of Gastric Cancer

As mentioned previously, the prognosis for gastric cancer is poor due to late-stage detection of cancer (Fung, 2018). If found early, endoscopic resection, surgical removal of the tumor, is recommended. Unfortunately, this treatment isn't one hundred percent effective due to recurrent tumor development shortly after treatment in three to ten percent of patients. Moreover, predictions as to which patients are likely to have recurrent cancer have not been successful, requiring yearly endoscopies to determine whether a tumor has developed (Sato et al., 2019).

Treatment of H. pylori - Benefits and Drawbacks

Since most individuals with H. pylori are asymptomatic and complications are not usually prevalent, treatment is not always necessary. Current medical practice is to treat all those who test positive. Testing is recommended for those with a family history of gastric cancer and those who live in geographical locations with high incidence and prevalence rates of gastric cancer, as well as those with symptoms (Crowe, 2019). Early detection and treatment of gastric cancer are crucial for survival; therefore, prevention is a major factor (Tanaka et al., 2022). However, many individuals infected with H. pylori do not develop complications such as gastric cancer or ulcers. Furthermore, it generally takes more than thirty years for H. pylori infection to progress to gastric cancer (Sato et al., 2019).

Perhaps instead of testing and treating all those in the above-mentioned categories, testing can be confined to specific parameters. ,Although more likely to develop complications, these individuals may still be asymptomatic and not endangered. H. pylori is currently detected via a urease breath test, a stool test, or an endoscopy (Crowe, 2019). It is also suggested that there are benefits to the inhabitance of H. pylori, and eradicating it unnecessarily isn't suggested. Moreover, H. pylori infection is not always easily treated as it is often resistant to antibiotics requiring multiple rounds of treatment. Tests for successful eradication are common practice (Jonaitis et al., 2021). Frequent use of antibiotics for unnecessary reasons is not recommended. Testing for H. pylori should perhaps include blood work in addition to standard detection methods. Testing can include markers of elevated gastrin, CagA, pepsinogen, etc., to determine if the bacterium is causing harm to the one infected.

A cost-effectiveness study that took place in China analyzed the monetary benefits of testing the general population above the age of forty for H. pylori. The researchers compared the cost of testing and treating the individuals positive for H. pylori to the cost of treating those with gastric cancer due to undiagnosed and untreated H. pylori. They concluded that testing their population did not prove to be beneficial monetarily. The study was done on both males and females but suggested that testing males only might be beneficial since gastric cancer is more prevalent in men (Xie et al., 2008).

Another study of individuals with H. pylori focused on those who had close relatives with gastric cancer. The researchers compared those treated with antibiotics and a proton pump inhibitor to those given a placebo. The authors reported that the eradication of H. pylori reduced gastric cancer by fifty-five percent. Additionally, those with successful eradication of H. pylori were at a seventy-three percent lower risk of developing gastric cancer. Those with unsuccessful eradication were at comparable risk to those who took the placebo. Participants in this study were monitored for slightly over nine years post-treatment (Choi Il Ju et al., 2020).

Esophageal Consequences and other Potential Benefits

One school of thought believes that CagA positive strains of H. pylori are actually beneficial for those with GERD in preventing Barrett's esophagus and adenocarcinoma of the esophagus (Mishra, 2013). Significant differences aren't observed with those who have GERD or Barrett's esophagus in regard to the prevalence of H. pylori; however, a study found all those with long segmented Barrett's esophagus lacked CagA positive strains of H. pylori. This suggests that CagA strains lower the acidity in the stomach, which causes less damage to the esophagus when gastric juice leaks through the sphincter. Eradication of H. pylori reduces the pH of the stomach, leading to Barrett's esophagus and adenocarcinoma (Vaezi et al., 2000).

On the other hand, another study showed that patients with H. pylori eradication were not found to have a significant impact on the erosion of the esophagus (Na et al., 2020). However, the study did not mention if the strains of bacteria were CagA positive or not, which can cause discrepancies. If they are negative for CagA, then the strain is less pathogenic, does not alter the acid level in the stomach, and would therefore make sense not to have an impact on symptoms or progression of GERD.

Aside from esophageal benefits, other advantages have been noted. Some research has shown that the presence of H. pylori has a protective effect on asthma as well as decreased diarrhea in children (Mishra, 2013).

Conclusion

H. pylori is a precursor for gastric cancer. The various means through which a malignant tumor develops have been outlined. Knowing the damage H. pylori causes, some of the symptoms of H. pylori, such as gastritis and iron-deficient anemia, can be understood. While prevention of gastric cancer is crucial as many lives are lost each year, eradicating H. pylori from all those who test positive may have consequences. Eradicating H. pylori to prevent complications that seldom occur has to be weighed against the benefits of its presence in preventing other complications.

Owing to the high resistance associated with traditionally-used antibiotics for H. pylori infection, other medications are being researched that target specific pathways that H. pylori optimize. Menadione, a laboratory-manufactured vitamin K (often referred to as K3), has been found to demonstrate antibacterial effects by preventing NF-kB from being activated, reducing inflammation, preventing the expression of VacA, and so forth (Min Ho Lee et al., 2019). Other ways of combating H. pylori may help reduce antibiotic resistance.

Since H. pylori has been around for a long time and is present in most individuals, some argue that the bacterium is part of the normal gastric flora. "H. pylori is just one bug that is isolated from a bacteria-rich stomach environment. And, like many bacteria in our digestive system, it is not only harmless when kept in balance with the other microbes, but may even be beneficial (Mishra, 2013)."

Perhaps research should focus on early detection of gastric cancer and other preventative measures to help minimize mortality from gastric cancer. Focus on methods of treating late-stage gastric cancer will undoubtedly save many lives.

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