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Helicobacter pylori: the Progression of Gastritis to Stomach Cancer*

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Abstract. General Background: Gastric cancer remains one of the most prevalent malignancies worldwide, with nearly one million new cases and over 700,000 deaths annually, largely linked to Helicobacter pylori infection. This gram-negative bacterium colonizes the gastric mucosa, causing chronic gastritis that can progress to malignancy. Specific Background: H. pylori is recognized as a Class I carcinogen by the International Agency for Research on Cancer due to its strong association with gastric adenocarcinoma. The infection triggers inflammatory and genetic responses that facilitate carcinogenesis through bacterial, host, and environmental interactions. Knowledge Gap: Despite decades of research, the molecular mechanisms linking H. pylori virulence factors to gastric epithelial transformation and the synergistic role of host and environmental cofactors remain insufficiently elucidated. Aims: This study reviews how H. pylori infection progresses from gastritis to gastric cancer by detailing bacterial virulence determinants, host inflammatory responses, and environmental contributors. Results: Key virulence factors such as CagA, VacA, BabA, and OipA disrupt epithelial integrity, modulate signaling pathways (e.g., NF-κB, Wnt/β-catenin), and trigger cytokine overexpression, fostering neoplastic changes. Novelty: The review integrates molecular, immunologic, and environmental dimensions of H. pylori pathogenesis, highlighting their collective role in carcinogenic transformation. Implications: Understanding these multifactorial mechanisms underscores the need for early detection, eradication therapies, and targeted prevention strategies to reduce gastric cancer mortality.

Highlights:

1. H. pylori infection can progress from gastritis to gastric cancer through chronic inflammation and mucosal damage.
2. The bacterium's virulence factors and host immune response play crucial roles in disease progression.
3. Early detection and eradication of H. pylori are vital to prevent gastric cancer development.

Keywords: Helicobacter Pylori, Gastritis, Gastric Cancer, Virulence Factors, Cytokines

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Introduction

More than half of the world's population are infected with Helicobacter pylori (H. pylori). The prevalence of H. pylori infection and the genotype of H. pylori virulence factors differ substantially in different parts of the world. The prolonged survival of H. pylori within the hostile stomach environment for decades results in damage to the gastric mucosa and changes in the pattern of release of gastric hormones thereby affecting the physiology of?the stomach (6-8). H. pylori has several virulence factors with which it controls host inflammation and initiates many "hits" to the stomach mucosa, resulting in chronic gastritis and peptic ulcers.

Gastric cancer (GC) and gastric MALT lymphoma are some of the late complications of H. pylori infection. Hence, H. pylori has been classified as a class I carcinogen by the International Agency for Research on Cancer [2, 3]. The specific pathways between H. pylori infection and the development of gastric cancer remain unclear, although there is robust evidence that the two are a cause-and-effect relation. H. pylori-mediated gastric mucosa cancer formulation proceeds through intricate interaction between the bacterium, host and environmental components as evidenced from the studies performed over two decades. H. Pylori is also able to induce an array of signalling networks [4].

Helicobacter pylori infection

Helicobacter pylori infects grater than 50% of the world’s population and is one of the most common infections among humans. Infestation prevalence varies considerably as a function of socioeconomic and hygienic conditions (more than 80% in rural developing areas, less than 40% in urban developed ones). >85% of H. pylori infections are acquired in childhood. Most infected individuals remain asymptomatic; however, up to 30% of these develop mild and severe upper gastrointestinal diseases including gastritis, peptic ulcers, gastric cancer and MALT lymphoma [5],[6].

Helicobacter bacteria are the only known microorganisms that can survive in the acid-filled region inside the stomach. It is thought that the Helical form the bacterium Helicobacter (hence the name) has taken, evolved to enable it to burrow in and grow inside of mucus lining human stomach epithelial tissue and mucous. It is thought to be acquired in young childhood and if unchecked, lifelong despite inducing immunity through both innate and adaptive immune systems [7].

Epidemiological evidence has demonstrated that from its discovery in 1984, H. pylori is the most common cause of infection-related cancers [8, 9]. It has been listed as a group I carcinogen [10]. Although the stomach is an acidic environment, the gram-negative bacterial pathogen H. pylori is able to grow in its gastric epithelium by hydrolyzing urea using a urease such that ammonia is released and the local pH becomes neutralised. Whilst an appreciable number of H. pylori infected individuals do not have a clinically apparent disease, chronic infection may result in inflammation of the stomach lining. It has been reported that about 10% of patients are evolved to peptic ulcers among those infected with this infection and a tiny population, ranging from 1-3%, develop gastric adenocarcinoma.[11,12]

Stomach carcinoma

Stomach cancer is diagnosed in nearly one million people annually with approximately 700,000 deaths from gastric adenocarcinoma [13]. Stomach cancer is the most common form of it in many areas of the world; in Japan, rates are more than ten times those recorded in the US. The absence of early typical symptoms commonly leads

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to late diagnosis of gastric cancer, and most patients are diagnosed after invasion of the muscularis propria. This may be one explanation for the less than 15% 5-year survival rate for gastric cancer in the US [14].

There are two histologic subtypes of gastric carcinoma, and were first reported in 1975. The first is diffuse-type gastric cancer, in which neoplastic cells of the stomach wall infiltrate without forming a glandular structure [15]. The natural history of intestinal-type cancer is the cascade of normal mucosa to chronic superficial gastritis, atrophic gastritis, intestinal metaplasia, dysplasia and adenocarcinoma [16]. Men are at 2 times' increased risk of being diagnosed with this type of GC as compared to women, and the median age is 50.42 for men and 47.7 for women [17],[18]. A decline of acid secretion may be responsible for the elevated risk of gastric cancer in the corpus-predominant gastritis group. Nevertheless, gastric antrum infections induce greater acid secretion and are a risk factor for duodenal ulceration[19].

Helicobacter pylori and stomach cancer

The association of H. pylori with oesophagal cancer has been controversial since a long time. Several studies have demonstrated that H. pylori infection carries a much higher risk of stomach cancer, such as 1,526 patients participating in a Japan study [20]. Kurashashi et al. found that the rate of gastric cancer in H. pylori-positive patients is about 3% higher than that in uninfected individuals, according to study from Uemura et al.

Chronic active gastritis, atrophying gastritis, metaplasia epithelia, intraepithelial neoplasia and invasive carcinoma are the steps to development of gastric cancer. H.pylori infection initiates and maintains the mucosal inflammation, which are considered as the two crucial steps for gastric cancer carcinogesis. As mentioned earlier, H. pylori is commonly acquired in the early years of life with subsequent lifelong exposure to this carcinogen. H. pylori infection poses a risk for the progression of gastritis and for developing a wide variety of H. pylori-associated diseases that can span from dyspepsia to even lethal complications. Atrophic gastritis, a group of interrelated pathologic processes characterized by shrinking of the stomach lining, varies according to geographical locations with higher susceptibility to gastric cancer [21]. For example, the lifetime risk of lacking stomach cancer in an individual (before reaching 75 years old) is about 0.6% in the USA. Conversely, the risk may exceed 20% in Japan and China [22, 23]. The H. pylori infection has to be eliminated in order to eliminate the risk of stomach cancer (the mucosa is healing but not eliminating the danger, it prevents this instead from rising, modifying the course of disease and reducing the risk of gastric cancer) [24 – 26]. The multistage precancerous process of gastric carcinogenesis is influenced by various host, bacterial, and environmental factors in an interaction relationship [27].

1. Bacterial virulence factors

CagA

The cytotoxin-associated gene (CagA), one of H. pylori's most potent virulence factors, is encoded by the cag PAI. Since its discovery in the early 1990s, CagA has been strongly linked to both stomach cancer and peptic ulcers. Compared to H. pylori strains lacking cag PAI, those containing it are more likely to cause gastritis and gastric cancer. By allowing the germs to adhere to the stomach epithelium of the host, H. pylori promotes the infection, adhesins and outer membrane proteins (OMP) aid in doing this [28]. Once bacteria adhere to the host, they need the type 4 secretion system (T4SS) to break through the epithelium. Proteins such as CagA, CagL, and CagY are required to construct the T4SS. At last, a syringe-like pilus structure injects CagA into the host

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epithelium [28].

T4SS needs several proteins for CagA to translocate into the host gastric epithelial cells. The association between T4SS proteins CagY and CagL and a5β1 stabilises the host cell. CagL stabilises the cell and helps secrete CagA into the host cell [29]. Carcinoembryonic antigen-related cell adhesion molecule (CEACAM) protein receptors are present in epithelial cells, and they bind to bacterial HopQ to cause CagA to translocate into gastric epithelial cells and an increase in proinflammatory mediators. In order for CagA to interact with the host cell's phospholipid, phosphatidylserine, and start its secretion into the cell, H. pylori also induces the host cell's plasma membrane to become visible [29].

The tyrosine-protein kinases Src (c-Src) and Abl (ABL1) are responsible for phosphorylating CagA at its EPIYA motifs, which are located in the carboxy-terminal after its cellular internalisation. In the human gastric adenocarcinoma cell line, following the phosphorylation and translocation of CagA, there is a morphological shift at the cellular level that results in cell elongation and scattering. The hummingbird phenotype is the term for this [29]. Host cell tyrosine kinase (SHP-2) and numerous other intercellular activators are activated by phosphorylated CagA. C-terminal src kinase (Csk) and extracellular signal-regulated kinases 1 and 2 (ERK 1 & 2) have been persistently activated as a result [30]. By prolonging the duration of ERK activation and dephosphorylating focal adhesion kinase (FAK), the CagA-SHP2 complex causes cell elongation in the human gastric cancer cell line [31]. FAK participates in the processes of cell migration and adhesion. Actin-binding proteins become dephosphorylated due to phosphorylated CagA's inhibition of c-Src's catalytic activity, which also causes cell elongation [32]. Epithelial tight junctions are further compromised when phosphorylated CagA interacts with the SHP-2 protein, inhibiting protease-activated receptor-1/microtubule affinity regulating kinase (PAR1/MARK kinase). It is well known that PAR1/MARK kinase maintains the junctional integrity and polarity of the stomach epithelium [33]. Numerous effects of CagA phosphorylation include actin cytoskeleton remodelling, enhanced cell proliferation, motility, activation of inflammatory cells, and transcription of mitogenic genes [34, 35].

VacA

Gastric epithelial cell barrier is disrupted, T-cell proliferation is inhibited, mitochondria damage is enhanced and cells are killed following exposure to vacuolation cytotoxin A (VacA). By employing these strategies, H. pylori is able to hide from immune responses and thus cause a long-lasting infection. VacA, one of the significant toxin proteins is delivered into target cell through H. pylori T4SS where it induces vacuolation. An anion-selective channel, VacA, is proposed to mediate this for the vesicular membranes. Enhanced Cl- ion transport via them produces an increase in intraluminal chloride concentration with a consequent osmotic swelling and vacuole formation in the cytoplasm of gastric cells. Additionally, VacA induces apoptosis, affects mitochondria and inhibits T-cell proliferation. It is hypothesized that VacA can induce cell death through enhancement of release of cytochrome c and reduction in mitochondrial electrochemical membrane potential by forming holes in the inner membrane of mitochondria.

It is not clear how VacA kills cells [36]. By binding to CD28 and T-cell receptor (TCR), VacA inhibits T cells activation. In the presence of IL-2, and in the absence of nuclear factors of activated T cells (NFTA), VacA is also capable to suppress T-cell proliferation. These properties allow H. pylori to escape from the host immune response and establish a chronic infection [37].

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HtrA

Helicobacter pylori secrete a virulence component called high-temperature requirement A (HtrA), which acts as a serine protease and a chaperone. Cell junction degradation results from the cleavage of E-cadherins on epithelial cells by H. pylori-secreted HtrA. It allows H. pylori to enter the stomach by breaking the gastric epithelial barrier [38]. HtrA's chaperone activities are necessary for protein regulation. HtrA refolds or degrades misfolded proteins. Overall, this permits the development and survival of bacteria in demanding environments [39].

BabA

For example, the outermembrane protein of Helicobacter pylori known as blood group antigen-binding adhesin (BabA) interacts with Lewis b blood group antigens (Leb) of host gastric epithelium [55]. H. pyloristrains expressing BabA are virulent and able to colonize greater than other bacterial strains [40, 41]. The binding of BabA to host epithelial cells is also responsible for translocating the CagA into the host cell using T4SS. The severity of H. pylori woes increase when CagA, VacA and BabA2 isotype are expressed. As virulence factors, they exert effect simultaneously. This deteriorates the occurance of gastric cancer and severe inflammation [41, 42].

SabA

The H. pylori adhesin sialic acid-binding adhesin (SabA) binds to the Sialyl-Lewis X antigen on the gastric epithelium. Up-regulation of Sialyl-Lewis X occurs when the host is undergoing an inflammatory response, and this acts at a means by which H. pylori is better able to adhere to the gastric mucosa in combination with SabA [43]. It is further established that SabA contributes to the risk of gastric carcinoma, atrophic gastritis and gastroduodenal diseases [43]. SabA is able to induce the host neutrophils by mimicking selectin function. Reactive oxygen species (ROS) are thereby generated and contribute to the continued inflammatory reaction [44].

GGT

Various roles for gamma-glutamyl transpeptidase (GGT) have been proposed. It not only causes gastric epithelial cells apoptosis but also favors the colonization of H. pylori, suppresses T-cell differentiation and proliferation [45]. GGT is found in H. pylori's outer membrane vesicles (OMVs). It has been linked with augmentation of gastric epithelial cell Il-8 and H2O2 production [46]. GGT also contributes to the depletion of glutamate and glutathione while enhancing ammonia and ROS synthesis. These give H. pylori the ability to derive for necrosis, apoptosis and cell-cycle arrest in epithelial cells leading to latter neoplasm[45].

OipA

HopH is the gene that encodes an outer inflammatory protein A (OipA), which is located on the bacterial exterior membrane and related to inflammation. H.process of acquiringlens OipA determines an enhanced inflammatory reaction relative to the H.lens negative strains. This results in a higher risk for stomach ulcers and gastric carcinomas [47]. Patients with premalignant gastric lesions had a higher prevalence of OipA+ in their biopsies compared to only gastritis patients [48]. The relationship of the interaction of OipA with gastric cells and the early events leading to skewing cell death towards apoptosis were demonstrated involving the activation of apoptotic cascade through Bcl-2 pathway. [49]. It has been demonstrated that OipA induce the expression of several pro-inflammatory cytokines, such as Il-1, Il-6 and Il-8. Furthermore, it also inhibits the maturation of dendritic cells and suppresses IL-10 release, further increasing the risk for

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developing GC [50].

2. Host factors

TNF-a

An H. pylori infection causes an increase in the pro-inflammatory cytokine tumour necrosis factor-a (TNF-a). It prevents stomach acid secretion, which permits H. pylori to endure and proliferate [51]. By stimulating the Wnt/β-catenin signalling pathway, TNF-a contributes significantly to gastric cancer [52]. It is well known that the Wnt pathway stimulates the proliferation of cancer cells and the development of embryos. For the correct development of key body tissues, it regulates embryonic cell migration, proliferation, body axis patterning, and cell fate specification [53]. An inflammatory response involving macrophage buildup is brought on by H. pylori infection. Macrophages secrete TNF-a, which stimulates Wnt/β-catenin signalling upregulation and ultimately aids in the development of gastric cancer [54].

IL-1β

Interleukin-1 β (IL-1β) is an IL-1 genotype that promotes inflammation. It is believed that IL-1β expression inhibits stomach acid output, leading to hypochlorhydria. Compared to H2 blockers and proton pump inhibitors, it has a stronger inhibitory effect on acid secretion. The colonisation of H. pylori is made possible by suppressing acid secretion, which increases the risk of gastric cancer and damages the mucosa.

IL-8

Strong chemokine interleukin-8 (IL-8) is released by gastric epithelial cells in reaction to H. pylori, a pathogen directly linked to gastric cancer. Increased IL-8 levels are associated with a worse prognosis and a more aggressive gastric cancer. C-X-C motif chemokine receptors 1 and 2 (CXCR1 and CXCR2) on endothelial cells are the sites of IL-8 binding. This increases angiogenesis and the survival rate of cancer by promoting the migration, proliferation, and survival of endothelial cells. Vascular endothelial growth factor (VEGF) is expressed when IL-8 binds to CXCR2, promoting new blood vessel development. The upregulation of cell surface receptors CXCR1 and CXCR2 promotes the ability of cancer cells to move and invade through the basement membrane. Through metalloproteinase production, IL-8 can damage the basement membrane, facilitating invasion and metastasis. The metastasis of gastric cancer is associated with IL-8-induced angiogenesis and invasion [56].

Il-10

The anti-inflammatory cytokine interleukin-10 (Il-10) reduces the cytotoxic inflammatory response and the cell-mediated immune response. The existence of Il-10 may more than double the likelihood of developing gastric cancer, according to a study by El-Omar et al. [51]. Sánchez-Zauco et al. conducted another investigation revealing that stomach malignancy generates its own Il-10, inhibiting anticancer responses. This explains why after the malignancy is excised, Il-10 levels drop [57]. According to Teymournejad et al., OpiA inhibits IL-10 secretion, which raises the risk of stomach cancer [50].

NFkB

One transcription factor that controls genes related to cell division, inflammation, and apoptosis is called Nuclear factor kB (NFkB) [58]. NFkB is located in the cytoplasm under normal circumstances, where it is blocked by IkB molecules. IkBs are broken down under stimulatory circumstances, allowing NFkB to go freely to the nucleus and start

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working [59]. Enzymes that regulate the activity of NFkB can be altered by cancer and inflammatory diseases [58]. Several virulence factors, such as cagPAI, CagA, and VacA, are produced by H. pylori and can activate the NFkB pathway. A buildup of mediators and inflammatory cells that support gastric cancer is caused by the activation of this pathway [60]. CagPAI-positive strains of H. pylori have a greater ability to trigger NFkB activity [59-60].

P53

One gene known to suppress tumours is P53, which controls the cell cycle and enhances tumour suppression [61]. About 40% of gastric tumours have P53 inactivation, a critical stage in the development of gastric cancer. The human double minute 2 (HDM2) protein downregulates P53. In the infected gastric cells, H. pylori activates serine/threonine kinase (AKT kinase), which phosphorylates HDM2. It is now possible for HDM2 to lower P53 in the stomach mucosa [62]. Moreover, CagA can directly cause HDM2 to become phosphorylated, which lowers P53 and increases the ability of DNA-damaged cells to survive [61,62]. Furthermore, it has been documented that H. pylori can induce cytidine deaminase production, which can result in a P53 mutation [62]. As a result, the p53 mutation might contribute to gastric cancer and could also be a useful biomarker and target for treatment [63].

ROS

Various host cells, such as neutrophils and epithelial cells, respond to the presence of H. pylori by generating reactive oxygen species (ROS). The neutrophil produces ROS to use NADPH oxidase to destroy the bacterium. Eradication of H. pylori is difficult since the infection is found in the lumen, and neutrophils are found within the tissue. This results in a persistent infection that damages the stomach mucosa and causes oxidative stress, inflammation, and gastric cancer in the end [64].

3. Environmental factors

Dietary salt is a major determinant of gastric adenocarcinoma and high salt intake promotes carcinogenesis. According to epidemiological studies, there is a strong relationship between high salt intake and high prevalence of H. pylori infection and an increased frequency of development of stomach adenocarcinoma in the infected individual. Numerous studies have shown that both a high salt diet and H. pylori infection interact to increase the formation of premalignant or gastric carcinoma. This might be due to the increase of pro-inflammatory cytokines, i.e. interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). The molecular mechanisms that contribute to this synergism in cancer growth are not clear. The complementary action of H. pylori and high-salt on gastric cancer formation has been elucidated and excessive salt intake may contribute to the generation of CagA, which is one candidate carcinogen in H. pylori for gastric cancer induction. However, smoking may promote the carcinogenic activity induced by H. pylori infection [65-68].

Conclusion

Gastric adenocarcinoma is responsible for approximately 700,000 deaths annually and ranks as the second leading cause of cancer death. The main reason for the increase in stomach cancer cases is a gram-negative bacterium, Helicobacter pylori (H. pylori), which has the ability to penetrate and colonise the stomach mucosa by developing different gastrointestinal diseases, including gastritis, and gastric cancer. H.p spp possesses several virulent factors contributing to the attached and translocated absorption of bacteria into

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gastric epithelial cell. The human body's immune system responds to this bacteria by producing cytokines and chemokines, which can promote the development of stomach cancer. In addition, the impact of H. pylori on GC risk might be modified by environmental factors. Both smoking and a diet with high salt significantly increase the risk of getting stomach illness. H. pylori can lead to stomach cancer, so early identification and treatment is crucial. If stomach cancer is found, treatment is important. The development of an efficient treatment for H. pylori induced stomach cancer needs additional investigation in order to decrease the mortality due to this disease.

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