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REVIEW ARTICLE

Molecular Mechanism of *Helicobacter pylori*-Induced Gastric Cancer

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Abstract

Introduction Various types of cancers threaten human life. The role of bacteria in causing cancer is controversial, but it has been determined that the *Helicobacter pylori* infection is one of the identified risk factors for gastric cancer. *Helicobacter pylori* infection is highly prevalent, and about half of the world's population is infected with it.

Objective The aim of this study was the role of *Helicobacter pylori* in the development of gastric cancer.

Method We obtained information from previously published articles.

Results and Conclusion The bacterium has various virulence factors, including cytotoxin- associated gene A, vacuolating cytotoxin A, and the different outer membrane proteins that cause cancer by different mechanisms. These virulence factors activate cell signaling pathways such as PI3-kinase/Akt, JAK/STAT and Ras, Raf, and ERK signaling that control cell proliferation. Uncontrolled proliferation can lead to cancer.

Keywords *Helicobacter pylori* · Gastric cancer · Cytotoxin-associated gene A · Vacuolating cytotoxin A

Introduction

Cancer can ensue from the unusual proliferation of any of the different types of cells in the body [1]. Tumors can be benign or malignant. A benign tumor is a mass that is incapable of invading neighboring cells or metastasize, but the malignant tumor can spread to other tissues and organs (metastasis); thus, it is cancerous [2]. The development of malignancy is a multistep process, and many agents, including radiation, chemicals, bacteria, and viruses, have been found to cause cancer [3–5]. Most carcinogens such as radiation and chemical carcinogens operate by damaging DNA and causing mutations [6]. Tumor promoters increase cancer development by stimulating cellular proliferation. The cell proliferation leads to mutations that occur during normal DNA replication [7]. Examples of tumor promoters are estrogen hormone, infectious agents such as viruses and bacteria, and chemical agents such as tobacco [8]. In both sexes worldwide, lung cancer and female breast cancer are the most common cancer (11.6% of the total cases) followed by prostate cancer (7.1%), colorectal cancer (6.1%), and nonmelanoma of skin (5.8%), stomach (5.7%), and lip and oral cavity (2%) for incidence [9]. Approximately 15–20% of human cancers are caused by cancer-causing viruses [10]. Although the role of bacteria in causing cancer is controversial, studies have shown that some bacteria play a role in the development of cancer [11]. The association between *Helicobacter pylori* (*H. pylori*) infection and the development of gastric cancer has been well studied [12]. In developing countries, 70 to 90% of people carry *H. pylori* before the age of 10 years old, but in developed countries, the prevalence of infection varies from 25 to 50% [13]. *Helicobacter pylori* account for more than 60% of gastric cancers. Gastric cancers account for more than 8.2% of all cancer deaths worldwide [14]. The World Health Organization (WHO) has categorized *H. pylori* as a group 1 carcinogen [15]. *H. pylori* can now be identified by a rapid urease test, histological examination of biopsy specimens, serological test, and polymerase chain reaction technique [16]. The association of bacterial infection with various cancers is listed in Table 1.

Helicobacter pylori and Gastric Cancer

H. pylori is a gram-negative, motile, microaerophilic, and spiral shape bacterium [27]. The only natural reservoir of *H. pylori* is the human stomach [28]. *H. pylori* infection usually occurs in childhood and remains in the host's life without antimicrobial treatment [29]. The bacterium can be transmitted by person to person transmission by the oral-oral or fecal-oral route [30]. It is estimated that

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Table 1 The association of bacterial infection and cancers

Bacterium	Related cancers	References
Helicobacter pylori	Gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma	[17]
Salmonella typhi	Gallbladder cancer	[18]
Streptococcus bovis	Colon cancer	[19]
Chlamydia pneumonia	Lung cancer	[20]
Fusobacterium nucleatum	Colorectal cancer	[21]
Porphyromonas spp.	Colorectal cancer, oral squamous cell carcinoma, and pancreatic cancer	[22–24]
Capnocytophaga gingivalis	Oral cancer	[25]
Prevotella melaninogenica	Oral cancer	[25]
Escherichia coli	Colorectal cancer	[26]

50% of the world's human population is chronically colonized with *H. pylori*, and about 15% of people infected develop gastric ulcers [31]. However, even when the infection is asymptomatic, *H. pylori* infection can lead to peptic ulcer and gastric cancer [32]. Chronic gastritis *H. pylori* is asymptomatic, but the initial onset of the infection causes acute gastritis with hypochlorhydria, which may cause abdominal pain, nausea, and vomiting that resolve within a few days [33]. Epidemiological studies show that 2–3% of *H. pylori*-infected people develop gastric adenocarcinoma, and 0.1% will develop mucosa-associated lymphoid tissue (MALT) lymphoma [34, 35]. *H. pylori* penetrate the gastric mucosa by flagella, where the mucus layer protects the bacteria from the low pH of the stomach [36]. Over 20% of the *H. pylori* strains adhere to the surface of the gastric epithelium cells [37]. *H. pylori* binds to the gastric epithelium by adhesion factors such as the blood group antigen-binding adhesin (BabA), sialic acid-binding adhesin (SabA), the outer inflammatory protein A (OipA), and adherence-associated lipoproteins (AlpA/B) [38]. BabA is an outer membrane protein (OMP) that binds to the human fucosylated Lewis b antigen (Le^b) or terminal fucose residues on blood group O (H antigen), A, and B antigens present on the surface of gastric epithelial cells [39, 40]. The epidemiological investigations indicate that there is a relationship between the O blood group and gastric diseases [41]. SabA is another OMP protein that attaches to sialyl-Lewis x (sLe^x) and Lewis a (sLe^a) antigens [42]. Lewis and sialyl-Lewis antigens are fucosylated carbohydrate moieties [43]. The binding of the *H. pylori* outer membrane protein OipA to the epithelial cell receptor is unknown, but it is assumed that attaches to the integrins present in the cell membrane [44]. Integrins are cytoplasmic membrane receptors that attach cells to the extracellular matrix [45]. Targets of *H. pylori* AlpA/B are laminin, type IV collagen, fibronectin, and vitronectin, component of the extracellular matrix [38]. The *H. pylori* virulence factors that are implicated in the development of gastric cancer including cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), and outer membrane proteins OMPs [46].

CagA and Gastric Cancer

The *H. pylori* cag pathogenicity island (cag PAI) is one of the virulence factors that function in gastric cancer [47]. The cag PAI is about 40 kb DNA insertion element containing 27–31 genes that encode CagA gene and other genes that make up proteins forming the Cag type IV secretion system (Cag-T4SS) [48]. The Cag-T4SS delivers CagA into gastric epithelial cells [49]. Within the host cell, CagA can be tyrosine phosphorylated at glutamate-proline-isoleucine-tyrosine-alanine (EPIYA) motifs by host Src/Abl tyrosine kinases [50]. Phosphorylated CagA has been reported to interact with the SH2 domains (for Src homology 2) of SHP2 (SH2 domain-containing protein tyrosine phosphatase, Csk (c-terminal Src kinase), Grb2 (growth factor receptor-bound protein 2), and Crk- (CT10 regulator of kinase) proteins [51]. Phosphorylated CagA binds to SH2 domain-containing protein tyrosine phosphatase and activates this enzyme. Activated SHP2 induces activation of the Ras (for rat sarcoma virus)–ErK (extracellular signal-regulated kinases) signaling pathway leading to mitogenic response [52]. In the nucleus, ERK phosphorylates and activates the transcription activator ELK1 (for E-26-like protein-1) [53]. Activated ELK1 along with SRF (serum response factor) binds to serum response elements (SREs) and induces the expression of immediate early genes including c-Fos and c-Jun [54–56]. c-Fos and c-Jun make up the AP-1 (the activator protein-1) transcription factor that induces the expression of late genes and cell proliferation [57]. The AP-1 transcription factor activates the transcription of cyclin D [58]. Increased cyclin D-CDK4/6 (cyclin-dependent kinase) activity results in phosphorylation of the retinoblastoma protein (pRB) and inducing the release of E2F from the pRB-E2F complex [59]. E2F can induce entry into the S-phase of the cell cycle by expression of cyclin E [60, 61]. The activated cyclin-E-CDK2 complex phosphorylates minichromosome maintenance (MCM) helicase at the origin of replication to initiate DNA replication [62]. Abnormal cell proliferation is an important property of cell transformation [63] (Fig. 1).

After entering into the gastric epithelium cell, the non-phosphorylated CagA interacts with E-cadherin (epithelial cadherin) in which results in the dissociation of E-cadherin and β-catenin complex and accumulation of β-catenin in cytoplasm and nucleus [64]. Cadherins are proteins that are involved in selective adhesion between cells in tissues [65]. β-catenin bounded to α-catenin links cadherins to actin filaments at adherence junction [66]. β-catenin/Tcf (T cell factor) complex activates expression of the genes encoding cyclin D1 and c-Myc that leads to abnormal cell proliferation [67] (Fig. 2).

The non-phosphorylated CagA also interacts with Grb-2 (growth factor receptor-bound protein 2)-associated SOS (Son of Sevenless), a guanine nucleotide exchange factor, and activates the Ras/MEK/ERK pathway that results in cell proliferation [68].

Vacuolating Cytotoxin A and Gastric Cancer

All *H. pylori* isolates secrete vacuolating cytotoxin A (VacA) through the type V secretion system [69]. The VacA is first produced as a 140 kDa protein that forms the mature 88 kDa protein containing p33 (33 kDa) and p55 (55 kDa) after a two-step proteolytic cleavage [70]. The p33 domain of this protein forms a channel consisting of six VacA subunits for chloride transport, but the p55 domain is responsible for binding protein to cell surface receptors including the receptor protein tyrosine phosphatase, epidermal growth factor, sphingomyelin, fibronectin, and lymphocyte-associated antigen [71–74]. VacA channels are formed in the cytoplasmic membrane and then enter the membrane of the endosomes and mitochondria through endocytotic vesicles [75]. VacA protein can separate the tight junction of the epithelial cells in gastric mucosa, As a result, VacA crosses through epithelial cells [76]. VacA has various effects on the host cell including cell vacuolization, alteration in mitochondrial membrane permeability, inhibition of T-lymphocyte activation and proliferation, and activation cell signaling [76]. The membranes of VacA-induced vacuoles carry markers of late endosomes and lysosomes; therefore, VacA-induced vacuoles are derived from the endosome-lysosome pathway. It has been suggested that the formation of VacA anion channels and activation of ATPase in

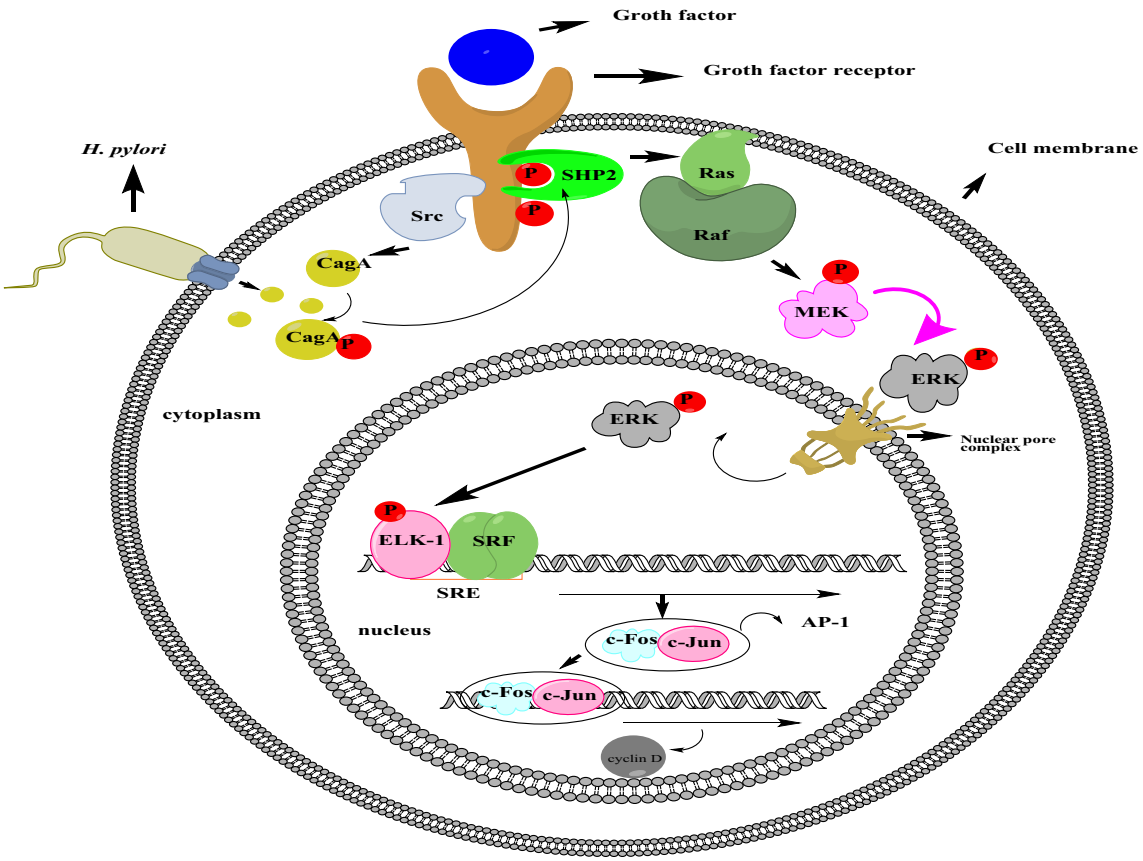

Fig. 1 Activation of Ras, Raf, and ERK by phosphorylated CagA. Binding of growth factor to a tyrosine kinase receptor leads to autophosphorylation and formation of binding sites for the SH2 domain of SHP2. Activated SHP2 activates the Ras. The activated Ras-GTP complex then activates the Raf protein kinase. Raf phosphorylates and activates the protein kinase MEK that in turn activates ERK. Activated ERK is translocated to the nucleus, where it phosphorylates the transcription factor ELk1. Activated ELK1 along with SRF binds to SRE and induce the expression of c-Fos and c-Jun genes. The ELK1-SRF complex transcription factor activates the transcription of cyclin D. Increased cyclin D causes cell proliferation. Src activates CagA that activates SHP2. Activated SHP2 causes uncontrolled cell proliferation

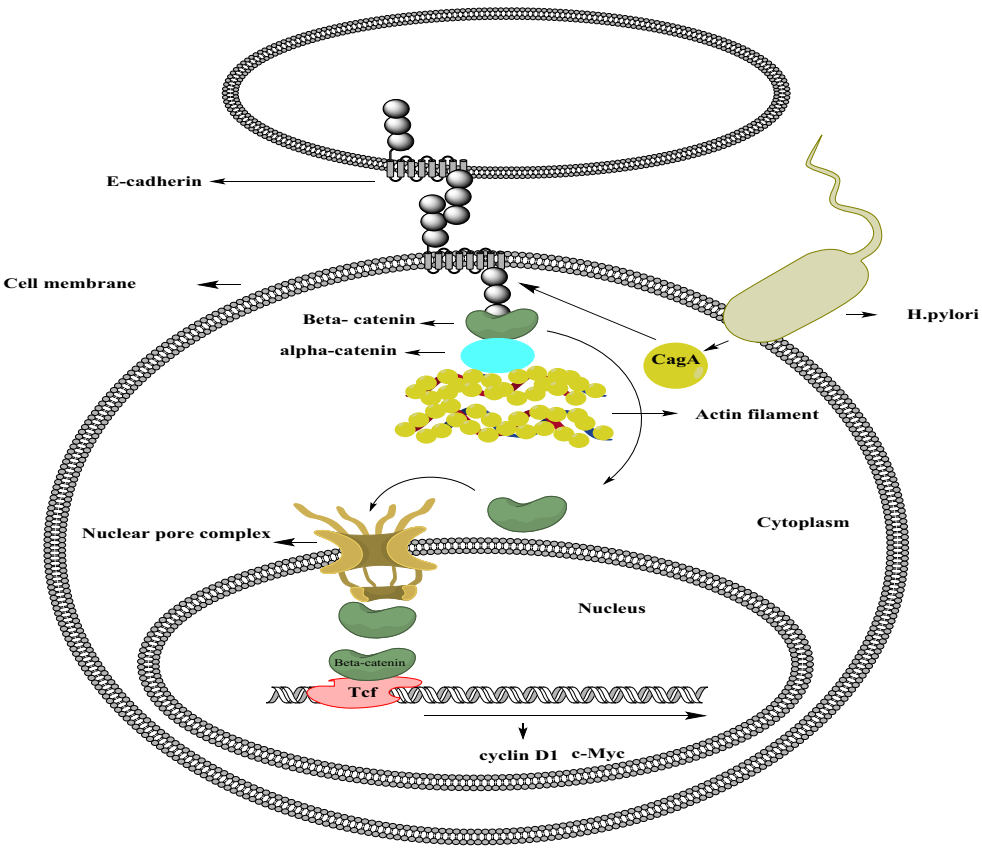

Fig. 2. Activation of β-catenin by the non-phosphorylated CagA. Non-phosphorylated CagA binds to E-cadherin and separates E-cadherin and β-catenin. β-catenin enters the nucleus and complexes with Tcf. β-catenin/Tcf complex activates expression the genes encoding cyclin D1 and c-Myc that leads to abnormal cell proliferation.

endosomal membranes leads to the osmotic swelling and the formation of vacuoles from late endosomes [76, 77]. VacA affects the β-catenin signaling pathway therefore, may play a role in the oncogenic potential of *H. pylori* [78]. VacA activates Akt (also called protein kinase B) via PI3K (phosphatidylinositol 3-kinase) that phosphorylates GSK3β (glycogen synthase kinase 3β) [79]. Akt is phosphorylated and activated by two protein kinases called PDK1 (3-Phosphoinositide-dependent kinase 1) and mTORC2 (mammalian target of rapamycin complex 2) that also bind to PIP3 [80]. The GSK-3β regulates cell proliferation and survival, which is inhibited by Akt phosphorylation [81, 82]. GSK3 is constitutively active under resting conditions [83]. In the absence of the ligand, β-catenin is phosphorylated by GSK3β in a cytoplasmic complex containing auxin, APC (the adenomatous polyposis coli protein), and β-catenin [84]. Then, the phosphorylated β-catenin is ubiquitinated and degraded into the proteasome [85]. In the presence of VacA, GSK3β is inactivated and leads to the accumulation of β-catenin in the cytoplasm [86]. The β-catenin enters the nucleus where it acts as a coactivator TCF (T cell factor) and LEF (lymphoid enhancer factor) transcription factor for activating transcription of β-catenin-dependent genes such as cyclin D1 [67, 87]. Overexpression of cyclin D1 is associated with cancers in humans [88] (Fig. 3).

Helicobacter Outer Membrane Proteins and Gastric Cancer

Three *H. pylori* outer membrane proteins (HomB, HopQ, and HopH (OipA)) are associated with gastric cancer [89, 90]. The specific outer inflammatory protein antigen (OipA) receptor has not been identified [91]. The OipA of *H. pylori* stimulates the phosphorylation of signal transducer and activator of transcription 1 (STAT-1) [92]. The nonreceptor tyrosine kinase associated with cytokine receptor so-called Janus kinase (JAK) phosphorylates the STAT. This pathway is called the JAK/STAT signaling pathway that is stimulated by cytokine [93]. Phosphorylated STAT1 forms a homodimer in the cytoplasm, and then it is transferred to the nucleus and binds to interferon γ-activated sequence (GAS) and stimulates the expression of interferon γ-induced genes. Interferon γ signaling can also lead to the phosphorylation STAT3 that binds to the GAS element and induces expression of inflammatory genes [94–96]. During inflammation, reactive oxygen and nitrogen species are produced to fight pathogens, but these chemicals can also destroy DNA, which in turn can initiate mutations and promote cancer [97]. The HopQ outer membrane protein binds to carcinoembryonic antigen-related cell adhesion molecule (CEACAM) present on the surface of the gastric epithelial cell and enables the transfer of CagA protein into the cell [98].

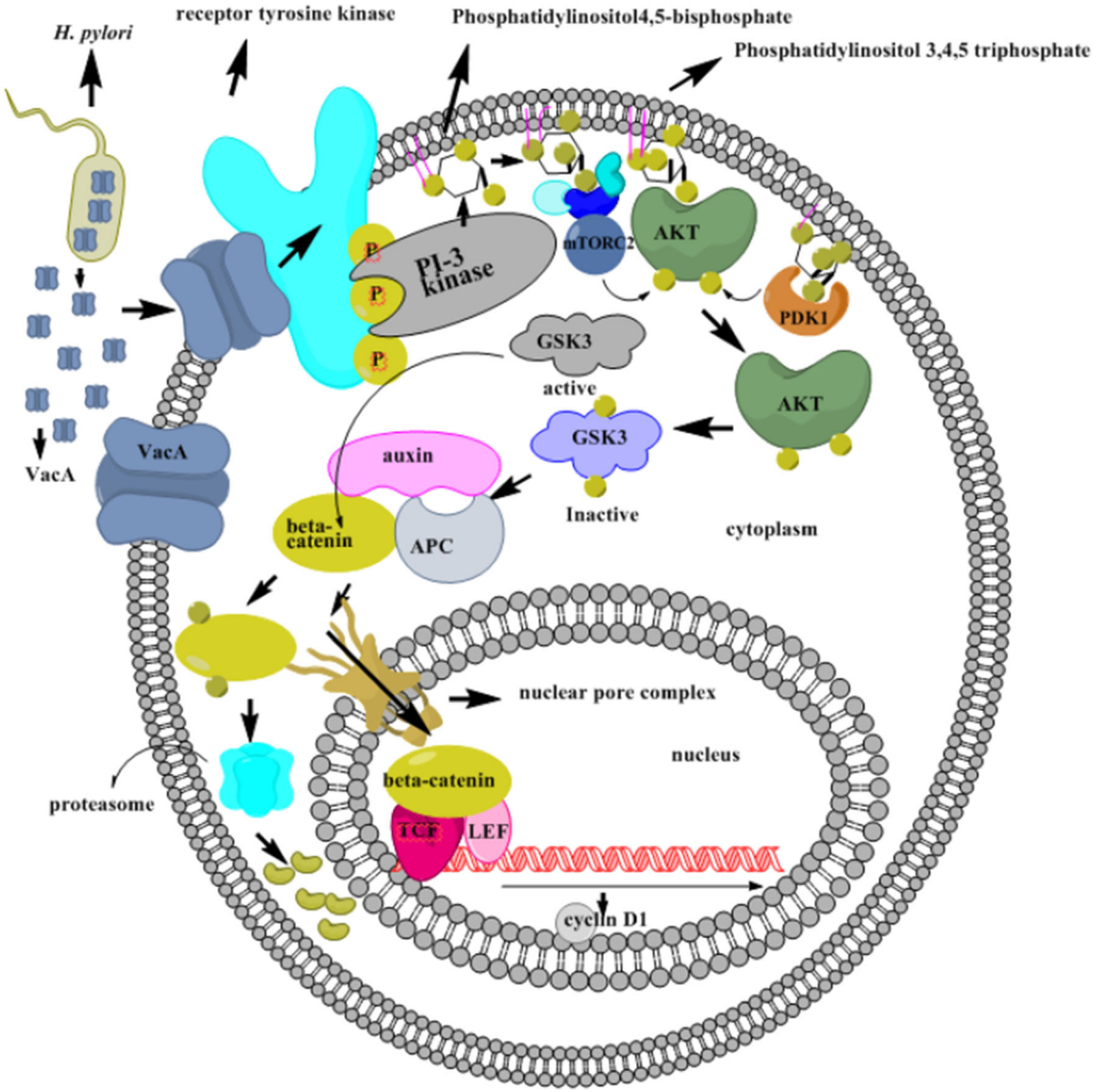

Fig. 3. Activation of the PI3-kinase/Akt pathway by VacA. PI 3 kinase is associated through its SH2 domain in the activated receptor tyrosine kinase. PI 3kinase phosphorylates the 3 position of inositol, converting phosphatidylinositol 4,5-bisphosphate to phosphatidylinositol 3,4,5-triphosphate. Akt binds to plasma membranes by binding to phosphatidylinositol 3,4,5-triphosphate. It is then activated as a result of phosphorylation by two other protein kinases (PDK1 and mTORC2) that also bind PIP3. The GSK-3 is inhibited by Akt phosphorylation. Inactivated GSK3β is inactivated and leads to the accumulation of β-catenin in the cytoplasm. In the presence of VacA, GSK3β is inactivated and conducts to the accumulation of β-catenin in the cytoplasm. The β-catenin enters the nucleus where it acts as a coactivator TCF and LEF transcription factor for activating transcription of β-catenin-dependent genes such as cyclin D1. High expression of cyclin D1 is associated with cancer.

The HopQ of *H. pylori* by facilitating the transfer of CagA protein into the cell is a major agent of gastric cancer [99, 100]. *H. pylori* attach to the gastric epithelial cell via the outer membrane protein HomB that is associated with gastric cancer [101, 102]. Binding of the HomB to the gastric epithelial cells is likely involved in causing inflammation [103].

Conclusion

H. pylori infection is one of the most common infections in humans that may progress to gastric cancer. This bacterium causes gastric cancer through its specific virulence factors such as cytotoxin-associated gene A, vacuolating cytotoxin A, and the types of outer membrane proteins. It activates

cellular proliferation signaling pathways, which makes laboratory diagnosis of infected individuals essential. Asymptomatic *H. pylori* infection is highly prevalent that can lead to gastric cancer, so it is recommended that people be screened for infection with this bacterium and receive appropriate drug treatment. The molecular mechanism of gastric cancer caused by *H. pylori* has not been fully elucidated, and further study is needed. *H. pylori* binds to gastric epithelial cells by the outer membrane proteins, so these proteins such as HomB, HopQ, and HopH are suitable candidates for vaccine development. A combination of a proton pump inhibitor (e.g., omeprazole), a macrolide (e.g., clarithromycin), and a beta-lactam (e.g., amoxicillin) is prescribed for 2 weeks to treat an infection caused by *H. pylori*. Given that CagA and VacA cause gastric cancer by activating cell proliferating signaling pathways, therefore, inactivating them could be a new therapeutic target for future studies.

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Compliance with Ethical Standards

Conflict of Interests The author declares that he/she has no conflict of interest.

Ethical Issues There are no ethical problems for this manuscript

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