The Mechanism of CagA and VacA in Gastric Cancer under the Tumor Microenvironment and Vitro Factors

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Abstract: Gastric cancer is closely related to the stomach microbiota, especially Helicobacter pylori. Numerous reports and clinical studies have shown that microbial behavior in the stomach may lead to pathological changes in the gastrointestinal tract of the host, which ultimately leads to the production and development of gastric cancer. This review outlines the major pathogenic processes of Helicobacter pylori in the stomach, specifically focusing on CagA, VacA, inflammatory pathways and oxidative stress. In addition, we describe the effects of some non-Helicobacter pylori factors, such as other microbiota, alcohol, and tobacco, on the carcinogenesis induced by Helicobacter pylori. The effects of family history are also taken into account. We hope that understanding the stomach microbiota will make it possible to more easily prevent, detect and treat gastric cancer.

Key words: Microbiota; Gastric cancer; Helicobacter pylori; CagA; VacA; Inflammatory pathway

Introduction

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer death worldwide [1]. About half of all cases and deaths due to GC occur in China, which causes a heavy burden on the Chinese healthcare system [2]. The stomach has been considered sterile, but in fact contains a variety of bacterial communities [3]. The best-known bacterium is Helicobacter pylori (H. pylori). In many areas of the world, including various parts of Asia, H. pylori infection rates are directly correlated with the rates of GC. [4]. However, while it has been known for several decades that H. pylori is related to GC [5,6], the mechanisms by which it induces carcinogenesis, and other factors that regulate the response to H. pylori infection, are still being uncovered.

We herein review recent research on the stomach microbiome and the mechanisms underlying H. pylori-induced carcinogenesis. These studies clearly demonstrate the pathological effects of certain microbial communities on the stomach [7]. As is well-known, H. pylori causes a variety of pathological changes in the host stomach, including chronic gastritis, atrophy, intestinal metaplasia and GC [8]. This review describes the recent findings regarding the major pathogenic processes associated with H. pylori in the stomach, focusing on cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), inflammatory pathways and oxidative stress. We also describe the effects of some non-Helicobacter pylori factors, such as other microbes, alcohol, and tobacco, on the induction of carcinogenesis by H. pylori. In addition, we take into account the effects of family history, and explore the impact of the host’s genetics on the H. pylori-mediated carcinogenesis. As more information becomes available about the stomach microbiota, we hope that it will become possible to prevent, detect and treat gastric cancer by using more advanced methods for gastric cancer screening and via microbial regulation.

The Carcinogenic Effects of H. pylori in the Human Stomach

The highly acidic environment in the stomach is lethal to many species of bacteria and parasites. However, there are others that have adapted to survive under such harsh conditions, including H. pylori. H. pylori has become symbiotic with humans [9], gradually evolving the ability to settle and survive in the highly acidic stomach of the human body [10]. Examples of such adaptations by H. pylori include the ability to change their shape and the number of flagella to maintain motility and chemotaxis in a viscous environment [11,12]. The bacteria also produce urease and other factors that help them adapt to the acidic conditions in the lumen [13] and mediate the preferential colonization of H. pylori at sites of gastric injury [14].

CagA

The cag pathogenicity island is a special fragment present in a 40 kb DNA sequence that encodes the CagA
protein and the type IV secretion system (T4SS) [15,16]. CagA is injected into the cytoplasm of gastric epithelial cells by *H. pylori* through the T4SS structure [17]. It has been demonstrated that CagA is a key factor involved in human chronic gastritis and ulcers, mucosa-associated lymphoid tissue lymphoma and GC [18]. Additionally, studies have shown that CagA-positive strains of bacteria are associated with a several-fold increase in the risk of GC compared with CagA-negative strains [19]. A meta-analysis further confirmed that individuals infected with CagA-positive *H. pylori* strains had an increased risk of developing GC [20,21].

CagA is a macromolecular cytoplasmic protein produced. Due to the structural differences in the C-terminal region, the molecule is subject to change [22], ranging from about 120 and 140 kD in length. CagA has a tyrosine phosphorylated region and a non-phosphorylated region [23]. Interestingly, the Glu-Pro-Ile-Tyr-Ala (EPIYA) motif present in the C-terminal region is a target for phosphorylation by Src family kinase (SFK) [24] and Abl families [25], while other regions are unable to undergo phosphorylation. CagA binds to various signaling proteins and causes dysregulation of multiple signaling pathways in a phosphorylation-dependent or -independent manner, inducing cancer via these pathways [26].

**Tyrosine Phosphorylation**

After tyrosine phosphorylation, segments C and D of EPIYA (EPIYA has four segments A, B, C, and D [27]) acquire the ability to bind to the Src-homology-2 domain containing PTPase (SHP2) [28] (Figure 1). SHP2 is a tyrosine phosphorylase that plays an important role in cell mitosis [29]. Although it has been suggested that East Asian CagA and Western CagA use different mechanisms to deregulate SHP2 [30], CagA binds to SHP2, activates SHP2 activity [28], enhances Ras-extracellular regulated protein kinases (Erk) signaling [31], and promotes abnormal mitosis. Studies have also shown that SHP2 is a proto-oncogene phosphatase [32], suggesting a link between CagA and GC. Researchers have shown that CagA interacts with C10 regulator of kinase (Crk) to play an important role in the reduction of gastric epithelial cell adhesion caused by *H. pylori* [33]. Crk-induced Src activation and the subsequent signaling of p38 mitogen-activated protein kinase (MAPK) promote the proliferation of sarcoma cells [34]. There is also an interaction between phosphorylated CagA and CagA-c-terminal Src kinase (Csk) [35] that leads to cell elongation called the “hummingbird phenotype” [36]. Csk phosphorylation inhibits SFK kinase activity, resulting in decreased EPIYA phosphorylation of CagA, which can effectively prevent tyrosine phosphorylation-dependent

![Figure 1 The CagA-positive H. pylori tyrosine phosphorylation pathway.](image-url)
overactivation of CagA activity. Although this has been suggested to have inhibitory effects on *H. pylori* [37], the bacterium remains closely associated with the development of GC.

**Non-Tyrosine Phosphorylation**

In the absence of tyrosine phosphorylation, there is dysregulation of various signaling pathways. In the phosphorylation-independent pathway, unphosphorylated CagA interacts with various signaling proteins, such as hepatocyte growth factor receptor (c-met), E-cadherin [38], growth factor receptor-bound 2 (Grb2) [39], and partitioning-defective 1b (Par1b) [40], and then activates the corresponding signaling pathway (Figure 2). *H. pylori* CagA targets the c-met receptor and enhances the cell motility. During the translocation process, CagA regulates cellular function by releasing the c-met receptor signal [41].

The occurrence of GC is inseparable from the process of inflammation. The CagA protein negatively regulates autophagy and promotes an inflammatory response to *H. pylori* infection. This inflammatory response is regulated by activation of the c-met-phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)-mammalian target of rapamycin (mTOR) signaling pathway [38]. The PI3K/Akt signaling pathway is strongly activated in GC [42].

*H. pylori* CagA also interacts with E-cadherin to promote beta-catenin signaling and the intestinal metaplasia of gastric epithelial cells [43], a precancerous lesion of the stomach. CagA interacts with Grb2, which activates the Ras/MEK/ERK pathway, leading to cell proliferation [39]. The interaction between CagA and Par1b inhibits Par1b kinase activity, affects the actin cytoskeletal system, and

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**Figure 2** The CagA-positive *H. pylori* non-tyrosine phosphorylation pathway. (a) CagA binds to c-met, releasing receptor signals to promote bacterial translocation. At the same time, the c-met pathway activates the downstream PI3K-Akt-mTOR pathway and participates in the inflammatory response. (b) CagA interacts with E-cadherin to induce beta-catenin signaling and promote the intestinal metaplasia of gastric epithelial cells. (c) CagA interacts with Grb2 to activate Ras/MEK/ERK, resulting in cell proliferation. (d) The actions of CagA and Par1b inhibit Par1b kinase activity and enhances the “hummingbird phenotype”. (e) CagA activates the highly conserved Wnt/beta-catenin pathway and promotes gastric cancer stem cell activity. (f) CagA induces NF-kB, decreases the expression of E-cadherin, and participates in tumor invasion. (g) CagA induces the JNK pathway and activates the STAT3-Akt signaling axis. At the same time, CagA inhibits p53 and induces RUNX3 methylation, leading to an increased risk of gastric cancer. In each of these processes, the nucleus is involved in the regulation of cellular activities.
enhances the size of cells with the hummingbird phenotype [40]. Neal JT et al. established a transgenic zebrafish model to study CagA, and found that it increases intestinal cell proliferation through activation of the Wnt pathway, leading to GC [44]. In general, the Wnt/β-catenin signaling pathway is highly conserved among species. Thus, *H. pylori* CagA-positive strains can promote the activity of human GC stem cells through the Wnt/β-catenin signaling pathway [45,46].

Kim SY et al. used eukaryotic expression vectors and showed that CagA induced NF-kappaB (NF-κB) activation and IL-8 release [47]. The NF-κB pathway is involved in tumor invasion and metastasis by reducing the expression of E-cadherin [48]. Recently, Wandler AM et al. used the JNK (c-Jun NH2-terminal kinase) pathway activation in a Drosophila model to demonstrate that CagA acts as an important mediator of activation of this signaling pathway [49,50], which ultimately promotes apoptosis or tumorigenesis. Further studies have found that there may be a carcinoogenic pathway linking the JNK-STAT3-Akt signaling axis [51]. *H. pylori* CagA was shown to promote the development of GC through activation of gastric STAT3 [52].

Interestingly, CagA can also interfere with certain tumor suppressors [53]. The experimental results described by Wei J et al. provided new evidence that the tumorigenicity associated with *H. pylori* infection is associated with CagA-mediated inhibition of p53 protein [54]. CagA enhances the degradation of p53 and down-regulates its activity [55]. Another study found that RUNX3 methylation was increased in poorly differentiated adenocarcinoma [56], thus decreasing the transcriptional activation of RUNX3 [57], thereby increasing the risk of GC. CagA has been drawing increasing attention in recent years, so it is possible that additional CagA-related effects will be discovered in the near future.

**VacA**

VacA is a vacuolar cytotoxin isolated from the supernatant of *H. pylori* culture medium, and is also a secreted toxin. VacA toxin is an 88 kDa pathogenic factor that consists of two domains; p33 and p55 [58]. Torres VJ et al. demonstrated that these two domains can interact to form a protein complex, and the binding of the mixture to the plasma membrane of mammalian cells is significantly enhanced compared to the binding of the VacA domain alone [59,60]. After entering eukaryotic cells, VacA leads to cell vacuolization [61]. *H. pylori* VacA forms an anion-selective channel in the planar lipid bilayer, which may induce a permeability imbalance in the intracellular acidic compartment [62]. Czajkowsky DM et al. found that when the pH is below 5, VacA combines with the anionic lipid bilayer to form a hexa-membrane-related complex, thereby forming pores [63]. This low pH-triggered pore formation may be a critical step in VacA activity [64], and the acidic environment of the stomach is conducive to this activity.

VacA has a variety of effects on cells, although the most important are altering the permeability of the plasma membrane and causing vacuolization of epithelial cells [65,66]. VacA induces autophagy, but the mechanism underlying this finding remains unclear [67]. Raju D et al. added VacA components to cultured gastric epithelial cells, and found that VacA could induce autophagy and regulate the degradation and circulation of cellular components in the cytoplasm [68]. VacA is also involved in biological reactions in the mitochondria. Jain P et al. found that *H. pylori* interfered with the morphological dynamics of mitochondria [69]. Chatre L et al. also suggested that *H. pylori* induces mitochondrial replication [70]. These changes are consistent with the progression of gastric lesions.

VacA also has immunomodulatory and inhibitory activities on various cells of the mammalian immune system, ensuring the persistence of the host *H. pylori* [71]. VacA can inhibit the activation and proliferation of T cells and B cells, and can interfere with the antigen expression of B cells [72]. It also prevents the normal maturation, antigen processing and expression of phagocytic cells, and interferes with intracellular killing and cytokine production [73]. The immune system is thus inhibited, ensuring continued infection with *H. pylori*.

VacA is similar to CagA with regard to its effects on gastric acid. Wang F et al. used freshly isolated rabbit gastric glands and cultured parietal cells to study the effects of VacA infection on the physiological function of parietal cells, and found that VacA penetrates into the apical membrane of these cells and induced hypochlorite production [74]. These effects echoed the earlier findings by Kobayashi’s team showing that VacA affected gastric acid secretion in guinea pig isolated wall cells [75]. Animal models have also revealed that VacA plays a role in promoting gastric pathology [76,77]. For example, VacA can cause damage to the gastric mucosa, increase inflammatory cells, and induce cancer [78].

The potential interaction of CagA and VacA is not well understood. However, VacA stimulates CagA degradation through an autophagy pathway, thereby reducing the half-life of CagA [79,80]. However, in gastric cells expressing CD44v9, autophagy is prevented, allowing the accumulation of CagA [81]. Therefore, the probability of cancer increases in cells that are invaded by *H. pylori*. In addition to CagA and VacA, genes such as iceA and babA2 also play a role in GC [82,83], mainly due to the increased risk of *H. pylori*-related diseases [84]. Moreover, there is a geographical dependence in terms of the roles and importance of the different gene products, providing some clues to the pathogenesis of *H. pylori*, and these agents are often closely related to the clinical outcomes [85].

**Inflammatory Response and Oxidative Stress Process**

The human immune system has innate and adaptive
immune responses to *H. pylori* [86], which can chronically proliferate and actively adapt to unfavorable parts of the stomach, making it difficult to eradicate [87]. Therefore, infection with *H. pylori* often leads to chronic inflammation, and oxidative stress may be caused by the inflammation. Although infected patients may remain asymptomatic indefinitely, *H. pylori* can induce an inflammatory response in gastric epithelial cells and may lead to the circulation of immune cells through various routes. Activation of NF-κB and up-regulation of IL-8 in gastric epithelial cells are considered to be critical for both *H. pylori*-induced chronic inflammation and GC [88,89]. Like the microbes associated with colorectal cancer-induced inflammation, *H. pylori* activates NF-κB by binding to the toll-like receptors (TLR) of epithelial cells and binding to myeloid differentiation factor 88 (MyD88) [90] (Figure 3). Lamb A et al. demonstrated that CagA and transforming growth factor-β-activated kinase 1 (TAK1) are essential for *H. pylori* to induce NF-κB activation [91]. CagA induction is mediated by tumor necrosis factor receptor-associated

**Figure 3** This image shows the carcinogenic process associated with *H. pylori*-related inflammation and oxidative stress. In the inflammatory response, *H. pylori* binds to MyD88 via TLRs and activates NF-κB. NF-κB activation activates the COX-2 and PGE-2 pathways and induces the release of cytokines such as TNF-α and IL-11, leading to gastric cancer. *H. pylori* releases CagA through T4SS. CagA stimulation leads to an increase in the SMO levels in the gastric epithelium and produces H2O2, leading to oxidative stress. H2O2 depolarizes the mitochondria and induces ROS production. The accumulation of ROS also depends on the toxin inhibiting the GSH pathway. ROS not only cause nuclear DNA damage, but also induce the up-regulation of IL-6, activate STAT3-NF-κB, and induce NF-κB activation mediated by TRAF6. CagA-dependent NF-κB activation can also be mediated through the PI3K/Akt signaling pathway. CagA negatively regulated autophagy and inhibits the anti-inflammatory effects of HO-1, leading to inflammation. VacA activates MAPK and NF-κB by releasing calcium ions. VacA also causes morphological changes in mitochondria, inhibiting gastric acid secretion and immune cell function. *H. pylori* can lead to the development of gastric cancer through all of these pathways.
factor 6 (TRAF6), which binds to TAK1 to induce NF-kB activation. CagA-dependent NF-kB activation can also be mediated through the PI3K/Akt signaling pathway [92]. The development of GC is considered to involve the combination of inflammation and oncogenes. Most tumors can induce cyclo-oxygenase (COX-2) expression, and NF-kB activation further increases the activity of the COX-2 and prostaglandin E2 (PGE-2) pathways. PGE-2 binds to the EP4 receptor [93], activates MAPK signaling [94], and induces the release of cytokines such as IL-11 and TNF-α. COX-2 also regulates E-cadherin expression via the NF-kB signaling pathway [48], which plays a role in the CagA oncogenic pathway.

In addition to the inflammatory response, the oxidative stress induced by *H. pylori* cannot be ignored. Chaturvedi R et al. recently reported that *H. pylori* expressing CagA leads to elevated levels of spermine oxidase (SMO) in gastric epithelial cells [95]. SMO decomposes polyamine spermine, which produces hydrogen peroxide (H$_2$O$_2$), leading to apoptosis and DNA damage. *H. pylori* CagA also oxidizes DNA by inducing SMO. These subpopulations of cells are often resistant to apoptosis, and therefore have a high risk of malignant transformation [96]. Hydrogen peroxide can depolarize mitochondria [97] and induce reactive oxygen species (ROS), which will continue to react with the nucleus [98]. ROS not only cause DNA damage, but also induce the upregulation of IL-6, which mediates STAT3 activation [99]. The STAT3 and NF-kB pathways are inextricably linked with the development of GC. Interestingly, after further studies, Tsugawa H et al. found that CagA accumulation in gastric cells expressing CD44 is due to VacA causing ROS accumulation and Akt activation by decreasing the intracellular glutathione (GSH) levels [80]. CD44 is a cell surface marker associated with cancer stem cells [108]. Together, these findings provide a possible molecular link between *H. pylori* and gastric carcinogenesis.

**Carcinogenesis Related to Non-*H. pylori* Factors in the Human Stomach**

Although *H. pylori* infection is considered to be a major risk factor for GC, approximately half of patients with gastritis are negative for *H. pylori* infection, and the abundance of *H. pylori* is decreasing in cancer patients. Lofgren JL et al. used a transgenic insulin-gastrin mouse model to confirm the association of gastric microbiota with the development of GC [109]. Sohn SH et al. used pyrosequencing to analyze the corpuscular microbiota and studied the possible roles of microbiota other than *H. pylori* in the development of GC [110]. Most studies on gastric microbiota have shown that the most common non-*H. pylori* populations are thick-walled bacteria, Bacteroides, and Fusobacterium [111]. Hsieh YY et al. found that the number of Clostridium in gastric cancer patients in Taiwan is significantly higher than that in other gastrointestinal diseases [112]. Moreover, recent research indicated that the average age of patients with GC has been decreasing [113], which may be related to disorders of microbial metabolism in the stomach. These results also suggest that *H. pylori* is the primary microbe related to GC, while a variety of other microbes play secondary roles [114,115]. In addition to the above microbial factors, alcohol and tobacco intake are also related to the incidence of GC [116]. Although various experiments are currently underway to investigate whether the interaction of alcohol with *H. pylori* can trigger GC [117], these studies are complex, and so far, the relationship between *H. pylori* and alcohol does not appear to be significant. The high incidence of CagA-positive *H. pylori* infection and precancerous lesions may also be related to the use of tobacco. Smoking can cause stomach damage, impair the healing of peptic ulcers, increase *H. pylori* infection, and increase the recurrence rate of peptic ulcers [118]. Therefore, tobacco increases the incidence of GC. Although other microbiota and alcohol may not necessarily directly affect the occurrence of GC, they may amplify the effects of *H. pylori*, accelerating the development of GC. This is an exciting area, and will also be the direction of our next phase of research on GC.

**H. pylori Induce Gastric Cancer in Patients with a Family History of GC**

Nishizawa T et al. performed single-factor and multivariate regression analyses that included the age, gender, body mass index, previous cancer history, family history of primary gastric cancer, and history of gastric ulcers in 206 patients with *H. pylori* infection. They concluded that family history is an independent risk factor for GC progression in patients with *H. pylori* infection [119]. At the same time, Sepulveda et al. found that patients with total gastritis with a family history of GC had higher lymphoid follicle density associated with *H. pylori* infection [120]. These two studies suggest that the interaction of *H. pylori* infection with a family history of GC increases the
incidence of GC in these individuals. This may be used as a theoretical basis for strategies to prevent GC. Because a family history of GC is associated with an increased risk of GC, the histological findings of gastritis may be suitable for the screening and monitoring of GC, especially in relatively young and at-risk populations. Infection with CagA-positive strains and records of family history may be useful markers for identifying patients at high risk for disease, as well as for prevention and early detection of GC.

**Outlook**

Microbiota is essential in the process of GC. Therefore, some measures against microbes (or that regulate specific populations of microbes) in the stomach may effectively reduce the incidence of GC. Leung WK et al. linked the treatment of *H. pylori* infection with lower risk of GC by analyzing data from Hong Kong public hospital databases [121]. Some laboratories attempted to inhibit IL-8 levels in the serum in a mouse model, and found that the pH of the stomach returned to normal levels, effectively inhibiting the viability of *H. pylori* [122]. Interestingly, some scholars have studied the anti-*H. pylori* effects of lactic acid bacteria (LAB). The concentration and morphology of organic acids were found to affect *H. pylori* infection [123]. In this way, doctors may be able to inhibit *H. pylori* activity by the delivery of new microbial populations. In addition, iron deficiency anemia [124] and high-salt [125] diets are factors that induce an increase in the invasiveness of *H. pylori*, so dietary interventions may be useful. However, the specific eradication of *H. pylori* seems to be the most promising approach to prevent GC. Human studies have confirmed that the eradication of *H. pylori* can reduce the risk of GC, a strategy that is more useful for patients without atrophic gastritis or intestinal metaplasia [126]. Of note, the presence of CagA-positive strains and a family history of GC may effectively eradicate *H. pylori* strains and records of family history may be useful markers for identifying patients at high risk for disease, which adds some accuracy to screening for gastric cancer. We anticipate that the technology used to both identify and eradicate *H. pylori* will be more targeted in the future, and the prevention and cure rates for GC will increase as a result of these and other interventions targeting the microbiome.

**Abbreviations**

- Akt, protein kinase B;
- C-Jun NH2-terminal kinase, JNK;
- C-terminal src kinase, Csk;
- Cyclo-oxygenase, COX-2;
- Cytotoxin-associated gene A, CagA;
- C10 regulator of kinase, Crk;
- Extracellular regulated protein kinases, Erk;
- Gastric cancer, GC;
- Glu-Pro-Ile-Tyr-Ala, EPIYA;
- Glutathione, GSH;
- Growth factor receptor-bound 2, Grb2;
- *Helicobacter pylori, H. Pylori*;
- Heme oxygenase-1, HO-1;
- Hepatocyte growth factor receptor, c-met;
- Hydrogen peroxide, H2O2;
- Lactic acid bacteria, LAB;
- Mitogen-activated protein kinase, MAPK;
- Mammalian target of rapamycin, m-TOR;
- Myeloid differentiation factor 88, myd88;
- NF-kappab, NF-xB;
- Partitioning-defective 1b, Par1b;
- Phosphoinositide 3-kinase, PI3K;
- Prostaglandin E2, PGE-2;
- Reactive oxygen species, ROS;
- Spermine oxidase, SMO;
- Src family kinase, SFK;
- Src-homology-2 domain containing ptpase, SHP2;
- Toll-like receptor, TLR;
- Transforming growth factor-β-activated kinase 1, TAK1;
- Tumor necrosis factor receptor-associated factor 6, TRAF6;
- Type IV secretion system, T4SS;
- Vacuolating cytotoxin A, vacA

**Conflicting Interests**
The authors declare that there is no conflict of interests.

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**References**
7. Wang LL, Yu XJ, Zhan SH, Jia SJ, Tian ZB, Dong QJ. Participation


Jabbour HN, Milne SA, Williams AR, Anderson RA, Boddy SC. Expression of COX-2 and PGE synthase and synthesis of PGE(2)in


Ricci V. Relationship between VacA toxin and host cell autophagy in Helicobacter pylori infection of the human stomach: a few answers, many questions. Toxins (Basel) 2016;8(7).


Utsch C, Haas R. VacA’s induction of VacA-Containing Vacuoles (VCVs) and their immunomodulatory activities on human t cells. Toxins (Basel) 2016;8(6).

Djekic A, Muller A. The Immunomodulator VacA promotes immune tolerance and persistent Helicobacter pylori infection through its activities on T-cells and antigen-presenting cells. Toxins (Basel) 2016;8(6).


113. Zhou F, Shi J, Fang C, Zou X, Huang Q. Gastric carcinomas in young (Younger than 40 Years) chinese patients: clinicopathology, family history, and postresection survival. Medicine (Baltimore) 2016;95(9):e2873.


history is an independent risk factor for the progression of gastric atrophy among patients with Helicobacter pylori infection. United European gastroenterol J 2017;5(1):32-6.


