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TOPIC HIGHLIGHT

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Role of *Helicobacter pylori* virulence factor cytotoxin-associated gene A in gastric mucosa-associated lymphoid tissue lymphoma

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Abstract

Helicobacter pylori (*H. pylori*) infection might initiate and contribute to the progression of lymphoma from gastric mucosa-associated lymphoid tissue (MALT). Increasing evidence shows that eradication of *H. pylori* with antibiotic therapy can lead to regression of gastric MALT lymphoma and can result in a 10-year sustained remission. The eradication of *H. pylori* is the standard care for patients with gastric MALT lymphoma. Cytotoxin-associated gene A (CagA) protein, one of the most extensively studied *H. pylori* virulence factors, is strongly associated with the gastric MALT lymphoma. CagA possesses polymorphisms according to its C-terminal structure and displays different functions among areas and races. After being translocated into B lymphocytes *via* type Ⅳ secretion system, CagA deregulates intracellular signaling pathways in both tyrosine phosphorylation-dependent and -independent manners and/or some other pathways, and thereby promotes lymphomagenesis. A variety of proteins including p53 and protein tyrosine phosphatases-2 are involved in the malignant transformation induced by CagA. Mucosal inflammation is the foundational mechanism underlying the occurrence and development of gastric MALT lymphoma.

Key words: *Helicobacter pylori*; Cytotoxin-associated gene A; Gastric mucosa-associated lymphoid tissue lymphoma; Lymphomagenesis; Molecular mechanism

Core tip: Cytotoxin-associated gene A (CagA) protein encoded by *cag* pathogenicity island of *Helicobacter pylori* is a bacterium-derived oncoprotein and is strongly associated with the gastric mucosa-associated lymphoid tissue (MALT) lymphoma. After being translocated into B cells *via* type Ⅳ secretion system in ATP-dependent manner, CagA deregulates several pathways in both tyrosine phosphorylation-dependent and -independent manners, and thereby promotes lymphomagenesis. Two important proteins, p53 and protein tyrosine phosphatases-2, are involved in the malignant transformation induced by CagA. In addition, mucosal inflammation is the foundational mechanism underlying the occurrence and development of gastric MALT lymphoma. However, the exact mechanism by which CagA promotes oncogenesis needs further clarification.

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INTRODUCTION

Helicobacter pylori (*H. pylori*), a spiral-shaped, microaerophilic, Gram-negative bacterium, infects approximately 50% of humans worldwide. *H. pylori* is associated with chronic active gastritis and peptic ulcers, is a risk factor for gastric cancer[1] and has been ranked as a class I carcinogen by the International Agency for Research on Cancer since 1994[2,3]. *H. pylori* infection might initiate and contribute to the progression of lymphoma from gastric mucosa-associated lymphoid tissue[4,5]. Clinical observations have shown that the eradication of *H. pylori* with antibiotic therapy can lead to regression of gastric mucosa-associated lymphoid tissue (MALT) lymphoma in 77.5%-94.0% of patients[6-9] and can result in a 10-year sustained remission in up to 64% of cases[10]. The eradication of *H. pylori* is the standard care for patients with gastric MALT. The results of a population-based study showed that the incidence of *H. pylori*-positive gastric MALT lymphoma had reduced sharply in the era of anti-*H. pylori* intervention[11]. This review summarizes the role of *H. pylori* cytotoxin-associated gene A (CagA) in the development and/or maintenance of gastric MALT lymphoma.

H. PYLORI CAGA IS CLOSELY RELATED TO THE DEVELOPMENT AND/OR MAINTENANCE OF GASTRIC MALT LYMPHOMA

The CagA protein, encoded by the cytotoxin-associated gene (*cag*) pathogenicity island, is one of the most important *H. pylori* virulence factors[12,13] and is causally linked to gastric MALT lymphoma. Fischbach *et al*[14] and Eck *et al*[15] determined that seropositivity of CagA was present in 89.0%-95.5% of patients with gastric MALT lymphoma, as tested by enzyme-linked immunosorbent assay and Western blot. The seroprevalence rate exceeded the prevalence of chronic active gastritis in the German population. The serological discovery of *cagA*-positive *H. pylori* isolates does not necessarily reflect the current colonization of the gastric mucosa because the immunoglobulin (Ig)A/IgG represents a past immune response. Mucosal-derived antibodies play an important part in the mucosal immune response. CagA-specific mucosal IgA and IgG antibodies occur in almost all patients with *H. pylori*-associated gastric MALT lymphoma[16,17]. Sumida *et al*[18] showed that in t(11;18)(q21;q21)-negative gastric MALT lymphoma patients, concentrations of anti-CagA IgG were significantly higher in the *H. pylori*-dependent cases than in the *H. pylori*-independent cases, and the *H. pylori*-dependent cases had a better therapeutic effect. The CagA protein can be detected in B lymphocytes in people infected with *cagA*-positive *H. pylori* strains[19]. Kuo further explored that CagA can be detected in the malignant B cells of *H. pylori*-associated gastric MALT lymphoma. The expression of CagA was evaluated using immunohistochemistry and confirmed using immunoblot analyses[20]. These findings suggest that gastric MALT lymphoma is associated with *H. pylori* strains expressing the CagA protein. Ohnishi and colleagues transfected C57BL/6 mice with a $cagA^{Hs}$ (humanized *cagA* gene) expression vector throughout the body or predominantly in the stomach to generate transgenic mice[21]. They performed immunoprecipitation, immunoblotting, histological examinations and other analyses of the gastric mucosa from 72-wk-old $cagA^{Hs}$ mice and determined that CagA induced abnormal proliferation of the gastric epithelial cells and hematopoietic cells, which was followed by the development of gastrointestinal carcinomas and lymphomas of B-cell origin. These results indicate that CagA is involved in the development of gastric MALT lymphoma, which provide the first direct evidence that CagA functions as a bacterium-derived oncoprotein in mammals[21].

MOLECULAR MECHANISM OF CAGA INVOLVEMENT IN GASTRIC MALT LYMPHOMA

The pathogenesis of lymphoma

Lymphomas are malignant tumors that originate in the lymphatic system. Lymphocytes proliferate in respond to the stimulation of persistent antigens and repeated infections in patients with immune deficiencies. The deregulation of the cell cycle and apoptosis is important in the pathogenesis of lymphoma. Lymphocytes that lack self-control divide faster than normal cells or survive longer than they should, proliferating in response to antigenic stimulation, which leads to the occurrence of unlimited proliferation and eventual lymphoma. Lymphocytes and lymphoid tissues do not normally exist in the stomach[22]. The onset of gastric MALT lymphoma is preceded by the acquisition of MALTs as a result of sustained *H. pylori* infection, which initiates the inflammatory lymphoproliferation[23,24]. The persistence of bacterial colonization, acting as immunologic stimuli, results in the recruitment of immune lymphocytes that migrate to and infiltrate the site of *H. pylori* infection in the stomach, which induce and sustain an actively proliferating B-cell population. Eventually, the formation of acquired lymphoid follicles and mucosal associated lymphoid tissues develop[25-27] (Figure 1). Much attention has been focused on the role of CagA in malignant transformation of the B cells. CagA may deregulate the host intracellular signaling transduction and lower the threshold for neoplastic transformation[28].

Structure of the CagA protein

CagA is encoded by the *cagA* gene within the *cag* pathogenicity island, a chromosomal region that simultaneously

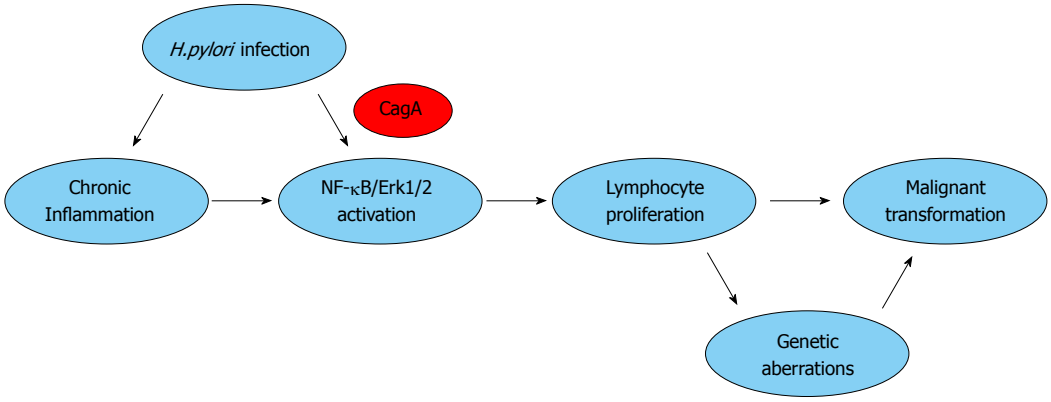

Figure 1 Oncoprotein cytotoxin-associated gene A is involved in the gastric mucosa-associated lymphoid tissue lymphoma development. *H. pylori*: *Helicobacter pylori*; CagA: Cytotoxin-associated gene A; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; Erk1/2: Extracellular signal-regulated kinase1/2.

encodes a type Ⅳ secretion system (T4SS) specializing in the transfer of CagA from bacteria to the target cells in an ATP-dependent manner[29,30]. CagA is the only known effector protein that is translocated by a T4SS[31-33]. Analyses of the DNA sequence and molecular phylogenic trees show that the CagA protein comprises a solid structured N-terminal region[31,34] and a variable, intrinsically disordered C-terminal region that is different among strains and exhibits scaffold/hub functions that are responsible for the morphogenetic activity of CagA[35]. The C-terminal domain contains repeated tandem five-amino-acid motifs of glutamic acid-proline-isoleucine-tyrosine-alanine (EPIYA). Within the variable region of CagA, there are different intervening sequences between the EPIYA motifs. One copy of EPIYA plus an intervening sequence is identified as an EPIYA segment. The tyrosine residues on the EPIYA (Y) motifs undergo tyrosine phosphorylation. Both the number and type of the EPIYA motifs determine the outcomes of cellular and gastric lesions[36,37]. Four unique types of EPIYA motifs (A, B, C and D) have been described based on their flanking amino acid sequences, which contribute to the CagA sequence polymorphism and geographical difference among strains. Almost all CagA contains both EPIYA-A and EPIYA-B motifs. The EPIYA-C motif is usually present in one to three repeats forming the typical Western CagA configuration of ABC, ABCC and ABCCC subtypes. In contrast, the EPIYA-D motif rarely repeats and thus prevalent East Asian CagA strains are ABD combinations[38]. The EPIYA-C and EPIYA-D motifs act as phosphorylation sites[39]. It is reported that increased number of EPIYA-C could enhance the binding ability to protein-tyrosine phosphatase-2 (SHP-2)[40]. Compared with EPIYA-C, EPIYA-D experiences a greater degree of tyrosine phosphorylation and stronger SHP-2-binding affinity, which leads to increased oncogenic potential[41,42]. Epidemiological data identified that the incidence rate of gastric MALT lymphoma is higher in East Asia than in Western countries[11,43-45]. East Asian might be prone to gastric MALT lymphoma at least partly, if not all, because most *H. pylori* strains are *cagA*-positive and nearly 90% of CagA carry EPIYA-D motif, 83.6% of which are of EPIYA-ABD genotype[46].

CagA deregulates intracellular signaling pathways in tyrosine phosphorylation-dependent and -independent manners to initiate pathogenesis.

Tyrosine phosphorylation-dependent pathway: CagA was directly injected from bacteria into attached gastric epithelial cells by a T4SS. Lin *et al*[19] further showed that the translocation of the CagA protein into human B lymphocytes could occur through the T4SS. The delivered CagA activates and stimulates the B lymphocytes, initiating the first step of the B-cell malignant stimulation. In host cells, CagA undergoes tyrosine phosphorylation by c-src/Lyn kinase on specific tyrosine residues of the EPIYA motifs[19,47]. The phosphorylated CagA deregulates the intracellular signaling pathways and initiates the malignant transformation of B lymphocytes. CagA specifically binds to intracellular target molecules, including the SHP-2 [Src homology 2 (SH2) domain containing phosphotyrosine phosphatase 2][39,41,48,49]. SHP-2, encoded by *PTPN*11, is a protein tyrosine phosphatase (PTP) and plays a vital role in normal hematopoiesis. SHP2 has two tandem SH2 domains, a PTP domain and a carboxyl-terminal tail which contains multiple tyrosine phosphorylation sites and is rich in praline motifs. In the inactive state, the N-terminal SH2 domain binds the PTP domain and hampers access of potential substrates to the active site. Thus, SHP-2 is auto-inhibited. In contrast, the N-terminal SH2 domain is free from the PTP domain by binding to target phospho-tyrosyl residues, catalytically activating the enzyme by relieving this auto-inhibition[50]. Mutation in *PTPN*11, an identified cellular proto-oncogene[51], or aberrant SHP-2 expression/activity positively correlates with the hyperproliferation of leukemic hematopoiesis[50,52]. SHP-2 functions as a vital adaptor protein in CagA signaling pathway[48,49]. However, *PTPN*11/

SHP-2 has dual roles in different cell types and its oncogenic role is tissue specific[53]. Most recent experimental data suggest *PTPN*11/SHP-2 as a tumor suppressor in hepatocarcinogenesis[54]. The above pathway depends on tyrosine phosphorylation of CagA.

Zhu *et al*[47] transiently transfected a recombinant retrovirus encoding an inserted *cagA* into conditionally immortalized B lymphocytes. The expressed and phosphorylated CagA was detected in the transfected B cells by Western blot and co-immunoprecipitation analyses, and CagA/SHP-2 complex was detected. The transfection of B lymphocytes with *cagA* significantly increased extracellular signal-regulated kinase1/2 (Erk1/2) phosphorylation, which is negatively regulated by MKP-1 and MKP-6, resulting in the phosphorylation of Bad at Serine 112 of CagA. Erk1/2, activated by CagA, can hamper apoptosis of B lymphocytes by inducing phosphorylation of Bad at Ser-112. *cagA* transfection did not alter the levels of the pro-apoptotic Bcl-2 and Bax. Immunofluorescence staining analysis displayed that CagA-activated Erk1/2 could translocate simultaneously to the cytoplasm and the nucleus, whereas serum-stimulated activated Erk1/2 was located only in the cytoplasm. The evidence indicates that the CagA-activated Erk1/2 can block apoptosis by activating the downstream target molecules, promoting the development of lymphoma. Lin *et al*[19] suggested that CagA translocation, following the phosphorylation of CagA which subsequently binds to and activates endogenous SHP-2, induces the activation of Erk1/2 and mitogen activated protein kinase and the up-regulation of the anti-apoptotic proteins Bcl-2 and Bcl-X_L in human B lymphocytes. The step prevents human B lymphocytes from apoptosis, allowing the lymphocytes to acquire survival ability, which contributes to the pathogenesis of lymphoma.

Tyrosine phosphorylation-independent pathway: Umehara *et al*[55] determined that CagA may block the cell cycle progression in the Ba/F3 and gastric epithelial cancer AGS cells, and inhibit the B lymphocyte apoptosis by impairing the p53 and JAK/STAT pathway. The enforced expression of CagA in the interleukin (IL)-3-dependent B-lymphoid cells functions as a G1 inhibitor, suppressing cell proliferation through the inhibition of JAK-STAT pathway and resulting in significant retardation of the G1- to S-phase cell-cycle transition. The IL-3 signal is mainly transmitted by the sequential activations of JAK and STAT. CagA offsets hydroxyurea-induced B-cell apoptosis by disturbing the tumor suppressor p53 accumulation. CagA inhibits the expression of p53 at the level of transcription. Meanwhile, *cagA*-positive *H. pylori* may be involved in the initial stage of gastric MALT lymphoma development, whereas it might not be necessary in the maintenance stage of lymphoma cell proliferation. CagA blocks apoptosis, promoting the accumulation of genetically abnormal cells that should otherwise be removed from the tissue. In IL-3-dependent B cells including BaF3, inhibitors of deoxyribonucleotide synthesis such as hydroxyurea induce apoptosis in a p53-dependent manner, whereas, DNA-damaging agents such as X-irradiation and cisplatin induce cell death in a p53-independent manner[56]. Interestingly, oxidative stress has been reported to be contributed to a variety of gastric disorders such as gastritis and ulcer diseases, especially gastric cancer[57,58]. Upon *H. pylori* infection and colonization, CagA might stimulate the response of gastric epithelial cells to oxidative stress and produce, mainly from neutrophils, reactive oxygen species (ROS) and/or reactive nitrogen species (RNS). Excessive ROS/RNS causes dysfunction of antioxidant defense mechanism in gastric mucosal, leading to DNA damage, accelerating cell death including apoptosis and subsequent cell proliferation, and resulting in the pathogenesis of gastric disorders as well as carcinogenesis[58]. Meanwhile, additional ROS and RNS may decline the expression of Runt domain transcription factor 3 (RUNX3), a marker of oxidative stress, which could restore after *H. pylori* eradication[58]. Therefore, RUNX3 acts as a tumor suppressor and is involved in *H. pylori* CagA-dependent gastric carcinogenesis. Moreover, some other molecules have been reported to be correlated with CagA-induced gastric carcinogenesis. Murine double minute 2 (MDM2) might promote pathogenesis of gastric cancer through inactivating the apoptotic and cell cycle arrest function of p53[59]. Yet, the role of RUNX3, MDM2 as well as oxidative stress production in CagA-induced gastric MALT lymphoma has been unclear and should be elucidated by further exploration. The malignant transformation from *cagA*$^+$ *H. pylori* infection into gastric MALT lymphoma should involve multiple steps. CagA has phosphorylation-dependent and -independent activities, and the biological effects of CagA in mammals depend on the cellular context. An imbalance between apoptosis and proliferation is involved in the pathogenesis and development of *H. pylori*-dependent gastric MALT lymphoma[60]. CagA inhibits apoptosis and impairs survival in the B cells, resulting in the transformation of MALT lymphoma[20] (Figure 2).

CONCLUSION

Mucosal inflammation is the basic mechanism underlying the occurrence and development of gastric MALT lymphoma. Infection with *H. pylori* induces inflammatory and immune responses in the gastric mucosa. The incapability of the host immune response to clear the bacterial pathogen results in a persistent infection and the subsequent development of chronic gastric inflammation[61]. The T-helper 17 (Th17) cells, whose hallmark cytokine is IL-17A, are important for the clearance of extracellular bacteria[62], and they play a role in infection control and precarcinogenesis. IL-17A may contribute to inflammation-associated carcinogenesis[62,63]. B7-H2 is among the newer members of the B7 family and is known to have a co-stimulatory function on T cell activity[64]. Recent *in vitro* and *in vivo* studies showed that *H. pylori* down-regulates B7-H2 (the positive co-stimulators required for an effi-

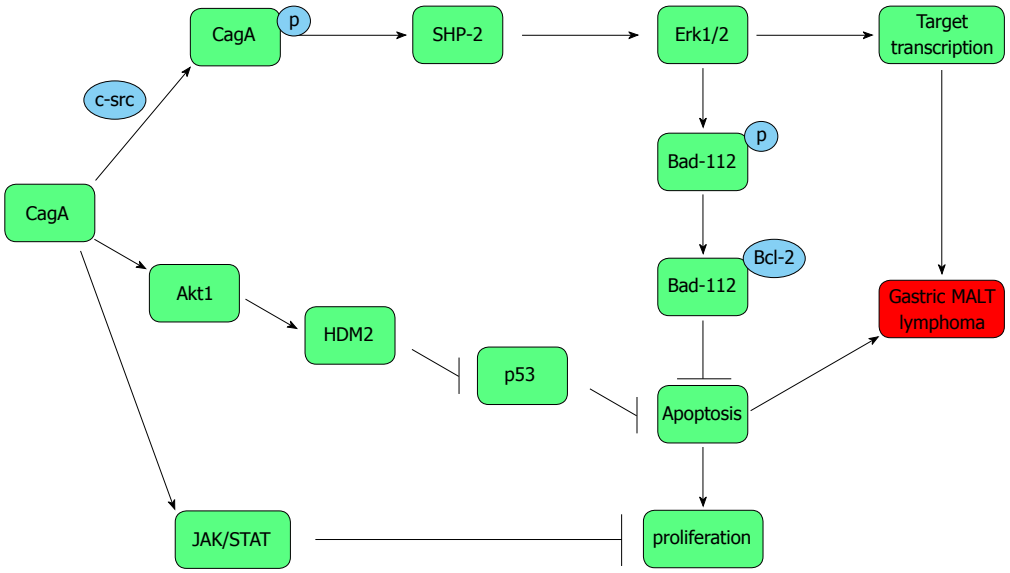

Figure 2 Cytotoxin-associated gene A deregulates intracellular signaling pathways in tyrosine phosphorylation-dependent and -independent manners to initiate lymphomagenesis. CagA: Cytotoxin-associated gene A; Erk1/2: Extracellular signal-regulated kinase1/2; MALT: Mucosa-associated lymphoid tissue; SHP-2: Protein-tyrosine phosphatase-2.

cient effector T cell response) in a CagA-dependent manner in gastric epithelial cells (GECs). CagA-dependent B7-H2 down-regulation in GECs suppresses the Th17-mediated immune response, contributing to outcomes of chronic gastric inflammation and persistent *H. pylori* colonization[65]. This process may be involved in gastric carcinogenesis, but the relationship with the development of gastric MALT lymphoma remains unclear. The activation of nuclear factor kappa-light-chain-enhancer of activated B cells and the up-regulation of IL-8 induced by *H. pylori* infections in B lymphocytes lead to the malignant transformation of B cells in a SHP-2-dependent and CagA-independent mechanism[66-68]. There is no direct evidence associating CagA, inflammation and gastric MALT lymphoma.

In recent years, microRNAs (miRNAs), a class of small non-coding RNAs that can modulate gene expression at the post-transcriptional level, have been implicated in *H. pylori*-dependent gastric carcinogenesis[69,70]. Much data suggest that miRNAs are important in fundamental cellular processes such as proliferation and apoptosis, and miRNAs can function as tumor promoters or suppressors[71]; the role of the miRNAs in the association between CagA and gastric MALT lymphoma remains unclear. Gastric MALT lymphoma is considered one of the best models of how infectious pathogens and genetic events lead to oncogenesis[72,73]. CagA functions as a typical bacterium-derived oncoprotein in gastric MALT lymphoma pathogenesis, but the molecular mechanism of CagA underlying the development of gastric MALT lymphoma should be further elucidated.

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