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Mini-review

Helicobacter pylori-induced gastric inflammation and gastric cancer

Fei Wang [a,1], Wenbo Meng [b,1], Bingyuan Wang [c,*], Liang Qiao [d,*]

[a] Department of Gastroenterology, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Province, China
[b] The Second Department of General Surgery, The First Hospital of Lanzhou University, Hepatopancreatobiliary Surgery Institute of Gansu Province, Clinical Medical College Cancer, Center of Lanzhou University, Lanzhou 730000, Gansu Province, China
[c] Department of Gastroenterology, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning Province, China
[d] Storr Liver Unit at Westmead Millennium Institute, The University of Sydney at Westmead Hospital, Westmead, NSW 2145, Australia

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ABSTRACT

Helicobacter pylori (*H. pylori*) infect over half of the world's population. The prevalence of *H. pylori* infection and the predominant genotype of *H. pylori* virulence factors vary considerably across different geographical regions.

H. pylori could uniquely persist for decades in the harsh stomach environment, where it damages the gastric mucosa and changes the pattern of gastric hormone release, thereby affects gastric physiology. By utilizing various virulence factors, *H. pylori* targets different cellular proteins to modulate the host inflammatory response and initiate multiple "hits" on the gastric mucosa, resulting in chronic gastritis and peptic ulceration. Among the long-term consequences of *H. pylori* infection is gastric malignancies, particularly gastric cancer (GC) and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. As such, *H. pylori* has been recognized as a class I carcinogen by the International Agency for Research on Cancer.

Despite a close causal link between *H. pylori* infection and the development of gastric malignancies, the precise mechanisms involved in this process are still obscure. Studies over the past two decades have revealed that *H. pylori* exert oncogenic effects on gastric mucosa through a complex interaction between bacterial factors, host factors, and environmental factors. Numerous signaling pathways can be activated by *H. pylori*.

In this review, we aim to elaborate on the recent developments in the pathophysiological mechanisms of *H. pylori*-induced gastric inflammation and gastric cancer.

1. Introduction

Helicobacter pylori (*H. pylori*) is perhaps one of the most common human infectious agents worldwide. Genetic sequence analysis has indicated that human being has coevolved with *H. pylori* for more than 58,000 years [1]. Since its discovery in 1982, *H. pylori* has been closely linked to a diverse spectrum of gastrointestinal diseases [2]. At present, *H. pylori* is considered the most common etiologic agent for infection-related cancers, which represent 5.5% of the global cancer burden [3]. The prevalence of *H. pylori* varies with the geographic regions, age, socio-economic status, education level, living environment and occupation. The vast majority of *H. pylori* infection occurs in the developing countries where up to 80% of the middle-aged adults may be infected [4]. In contrast, the world's average prevalence of *H. pylori* infection was reported to be 58% [5].

Although the majority of individuals infected with *H. pylori* remain asymptomatic throughout their life, essentially all develop chronic inflammation [6]. Among infected individuals, approximately 10% develops peptic ulcer disease, 1–3% progresses to gastric cancer (GC), and 0.1% develops mucosa-associated lymphoid tissue (MALT) lymphoma [7]. Of the various diseases that are closely associated with *H. pylori* infection, gastrointestinal malignancies are perhaps the most important entities requiring extensive studies. Understanding the molecular mechanism of *H. pylori*-induced carcinogenesis is important for developing new strategies against GC.

In this mini-review, we will describe epidemiology of *H. pylori* related gastric malignancies, discuss the factors affecting the susceptibility of *H. pylori* infection, and subsequent gastric carcinogenesis, and review the recent developments in the pathophysiological mechanisms of *H. pylori* induced GC. The frequently used abbreviations are listed in Table 1.

* Corresponding authors. Address: Department of Gastroenterology, The First Affiliated Hospital of China Medical University, Shenyang 110001, Liaoning Province, China. Tel.: +86 24 83282900; fax: +86 24 83282997 (B. Wang), Storr Liver Unit at Westmead Millennium Institute, The University of Sydney at Westmead Hospital, Westmead, NSW 2145, Australia. Tel.: +61 2 9845 9132; fax: +61 2 9845 9103 (L. Qiao).

E-mail addresses: wangby@medmail.com.cn (B. Wang), liang.qiao@sydney.edu.au (L. Qiao).

[1] These authors contributed equally to this work and share the first authorship.

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2. Epidemiology of *H. pylori* infection and gastric malignancies

H. pylori infection is by far the most important risk factor for gastric malignancies, among which gastric adenocarcinoma are presents the most common type (90%) [7]. In a recent study of 114 cases of histologically-proven GC from Eastern Libya [8], the overall infection rate of *H. pylori* was 63.2%, and the infection was particularly more common in intestinal type gastric adenocarcinoma (71.7%) and malignant lymphoma (66.6%) than in diffuse adenocarcinoma (55.3%).

The impact of *H. pylori* infection on gastric malignancies may depend on the anatomic location. Cancers of the proximal stomach (cardia and gastroesophageal junction) have different epidemiological and pathophysiological characteristics, and are not commonly found in high *H. pylori* endemic areas [9]. For example, adenocarcinoma derived from gastroesophageal junction may be associated with neither *H. pylori* infection nor Barrett's esophagus [10].

Gastric MALT lymphoma represents an extranodal lymphoma consisting mainly of morphologically heterogeneous small B cells. It is now well-understood that *H. pylori* infection is closely linked to the development of gastric MALT lymphomas. As revealed by a systematic review involving a total of 1,844 patients extracted from 38 studies, the average prevalence of *H. pylori* infection in MALT lymphoma was 79%, and the rate was higher in low-grade (79%) than in high-grade (60%) cases [11]. Eradication of *H. pylori* led to a complete remission in 60–80% of patients with MALT lymphoma [12,13] and a 10-year sustained remission in up to 64% of cases [14]. As such, eradication of *H. pylori* has become a standard of care for patients with gastric MALT lymphoma.

3. Mechanisms involved in the pathogenesis of *H. pylori*-induced gastric inflammation and carcinogenesis

H. pylori produce a variety of virulence factors that may dysregulate host intracellular signaling pathways and lower the threshold for neoplastic transformation. Of all virulence factors, *CagA* (cytotoxin-associated gene A) and its pathogenicity island (*Cag* PAI), and *VacA* (vacuolating cytotoxin A) are the major pathogenic factors.

3.1. Role of CagA in gastric inflammation and carcinogenesis

The *Cag* PAI is an approximately 40 kb locus composed of 27–31 genes. Several genes within this island encode the *CagA* protein and the Cag type IV secretion system (T4SS) [15]. The T4SS forms a syringe-like pilus structure by which *CagA* can be "injected" into the target cells. Binding to the ectodomain of α5β1 integrin is an essential step for the translocation of *CagA* into the host cells [16]. Once translocated into host cytoplasm, *CagA* may bind to the inner surface of the cell membrane and undergoes tyrosine phosphorylation at its glutamate-proline-isoleucine-tyrosine-alanine (EPIYA) motif by Src family kinases. The phosphorylated and unphosphorylated *CagA* interact with a number of host proteins to activate downstream signal pathways, such as the Ras/mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway [17,18], nuclear factor κB (NF-κB) pathway and β-catenin pathway. These changes will enhance the proliferative ability of the gastric epithelial cells.

Src-homology protein tyrosine phosphatase (SHP) 2 is not only an intracellular target for *CagA* but also a pivotal mediator for *CagA*-induced downstream signaling. In AGS cells (a gastric adenocarcinoma cell line), tyrosine phosphorylated *CagA* can specifically bind to SHP2 and provoke Ras-dependent and independent signaling via the SHP2-(Ras)-ERK (MAP-kinase) cascade. *CagA*-mediated SHP2 signaling leads to deregulation of epithelial cell polarity (characterized by cell elongation and scattering, the so called "hummingbird phenotype"). The interaction between *CagA* and SHP-2 also dephosphorylates and inactivates focal adhesion kinase (FAK), resulting in cell elongation [18,19].

Non-phosphorylated *CagA* has several molecular targets. Studies have shown that *CagA* could activate the hepatocyte growth factor/scatter factor receptor c-Met and adaptor protein Grb2 [20], induce phosphorylation of phospholipase C gamma (PLCγ) and impair the E-cadherin/β-catenin complex formation in a *CagA*-independent manner [21,22]. In addition, non-phosphorylated *CagA* could mediate the inhibition of the kinase partitioning-defective 1b/microtubule affinity-regulating kinase 2 (PAR1b/MARK2) to perturb atypical protein kinase C signaling, resulting in disruption of tight junctions and loss of cell polarity [23].

Much attention has been paid to the role of the C-terminal domain, which bears three EPIYA motifs that become tyrosine phosphorylated by Src and Abl kinases in eukaryotic cells. The N-terminus of unphosphorylated *CagA* targets the plasma membrane through interacting with several junction proteins (e.g., E-cadherin, *zonulaoccludens* 1 and junctional adhesion molecule A), resulting in disruption of the epithelial cell apical junction complex, loss of cell polarity and provoke pro-inflammatory and mitogenic responses. These processes are known to facilitate the malignant transformation and development of intestinal metaplasia [23]. In addition, *CagA* N-terminal domain interacts with multiple intracellular partners. For example, *CagA* alters the association between apoptosis-stimulating protein of p53-2 (ASPP2) and p53 to stimulate the proteasomal degradation of p53 [24], inactivates the gastric tumor suppressor Runt-related transcription factor3 (RUNX3) [25], and enhances tumor necrosis factor receptor-associated factor 6 (TRAF6)-mediated Lys 63-linked ubiquitination of transforming growth factor-β (TGF-β)-activated kinase 1 (TAK1) [26]. Moreover, the N-terminal domain of *CagA* contains the binding element to the ectodomain of α5β1 integrin, and thus is responsible for the translocation of *CagA* into the host cells [16].

3.2. Role of VacA in gastric inflammation and carcinogenesis

The vacuolating cytotoxin (*VacA*) is secreted by *H. pylori* via a type V autotransport secretion system. *VacA* is an 88 kDa protein comprised of the p33 and p55 subunits. The p33 (N-terminal, 33 kDa) forms an inner channel for chloride transport, while the p55 (C-terminal, 55 kDa) segments are indispensable for binding of the toxin to host cells [27].*VacA* has a variety of biological activities. It binds to host cells and is internalized creating severe "vacuolation" characterized by a collection of large vesicles that possess hallmarks of both late endosomes and early lysosomes. *VacA* can also be transferred to mitochondria where it causes the dissipation of mitochondrial transmembrane potential ($\Delta\Psi m$), cytochrome c release, and activation of pro-apoptotic factor Bcl-2 associated X protein (Bax), thereby leading to apoptosis [28]. During *VacA*-induced mitochondria perturbation, activation of dynamin-related protein 1 (DRP1) may play a critical role, as inhibition of DRP1-dependent mitochondria fission within the *VacA*-intoxicated cells inhibited activation of Bax and mitochondrial outer membrane permeabilization (MOMP), and prevented death of intoxicated cells [29]. Additionally, *VacA* can disrupt the tight connections of the epithelial cells and obstruct T lymphocyte activation and proliferation in the *lamina propria*. Disrupting autophagy is another mechanism by which *VacA* induces gastric inflammation and contributes to gastric carcinogenesis [30,31].

3.3. H. pylori induced inflammatory responses

Inflammatory disorders have been well recognized as the key risk factors for many types of cancers. *H. pylori* infection and the