https://muthmj.mu.edu.iq

Muthanna Medical Journal
2023; **10**(1):67-74

http://dx.doi.org/10.52113/1/1/2023-67-74

Virulence factors of *Helicobacter pylori*

Haifaa B. Najee [1], Shaimaa M.S. Zainulabdeen[1], Iman A. Atiyah [2]

Abstract

One of the most common cancers in both genders, gastric cancer is currently the fourth leading cause of cancer-related deaths globally. The interplay of hereditary and environmental variables, including *Helicobacter pylori* (H. pylori) infection, is linked to the etiology of stomach cancer. Due to a number of evasive mechanisms brought on by the virulence factors that the bacteria express, the invasion, survival, colonization, and stimulation of further inflammation within the gastric mucosa are all conceivable. To improve eradication efforts and stop the potential induction of carcinogenesis, it is essential to understand the pathogenicity mechanisms of *H. pylori*. This review focuses on the most recent research on the relevance between *H. pylori* virulence factors, subsequent carcinogenesis, and stomach premalignant lesions.

Keywords: Helicobacter pylori, Virulence factors, Mucosa-associated lymphoid tissue lymphoma (MALT)

* Correspondence author: haifaa.najee@mu.edu.iq
[1] Department of Microbiology, College of Medicine, Al-Muthanna university
[2] Department of Medical laboratories, College of Health and medical techniques, Sawa University
Received 26 December 2022, Accepted 15 February 2023, Available online 26 February 2023.

Introduction

The gram-negative, microaerophilic, spiral-shaped, flagellated bacterium *Helicobacter pylori* (*H. pylori*) may indeed change its form from spiral to coccoid, which is thought to be important for bacterial survival in the human gastric microenvironment [1]. While *H. pylori's* coccoid form gives the bacterium the capacity to colonize the mucus layer of the gastric epithelium, further increasing its invasiveness, the spiral shape promotes the bacteria's successful motility.

Moreover, *H. pylori* has the capacity to create biofilms that reduce its sensitivity to a number of medications, which increases the risk of antibiotic resistance mutations and complicates efforts to eradicate the bacteria [2].

Since 1994, both the World Health Organization (WHO) and the International Agency for Research on Cancer have designated *H. pylori* as a class I carcinogen linked to the development of gastric cancer (GC) [1,2].

Pathogenesis

Helicobacter pylori's pathogenicity had linked to a number of processes, but the host signaling pathway changes, the indirect inflammatory responses they cause in the gastric mucosa, and the direct epigenetic effects they have on the gastric epithelial cells are crucial [3]. Most of all people on earth have *H. pylori* in their stomach mucosa, and it actively manipulates host tissues to create an immunosuppressive environment that sustains chronic infection [4].

Earlier studies showed that *H. pylori* infection is adversely correlated with systemic inflammatory illnesses such asthma, lupus, inflammatory bowel disease, and eosinophilic esophagitis in the human population and in animal models [5]. Many gastrointestinal conditions, including severe gastritis, peptic ulcer disease, and gastric mucosa-associated lymphoid tissue lymphoma (MALT), can be brought on by *H. pylori*. The World Health Organization's International Agency for Research on Cancer (WHO/IARC) has classified it as a Category I carcinogen [6].

Virulence factors

Many effector proteins and toxins produced by *H. pylori* cause harm to the host's tissues. Chemokines that are released during an infection cause innate immunity to be triggered [7].

1. Vac A: the 88-kDa protein known as vacuolating cytotoxin type A (VacA) is made up of the p33 and p55 protein subunits. Vacuoles are formed by VacA in the epithelial cell of the host [8]. Because since vacA is varied, gastric cancer risk is increased by polymorphism at a particular gene location. The s region (signal region), which is at the end of the 5' region, the m region (middle region), and the intermediate region can be used to categorize the regions of vacA. (i region). Alleles from the s and m regions fall into the s1, s2, m1, and m2 categories [9]. The beginning of apoptosis is one of the important roles of VacA [10].

2. cagA: The cagA gene, which is found at the 30 end of cagPAI, produces the 128-kDa CagA protein [11]. CagA-positive *H. pylori* more dangerous than CagA-negative H. pylori [12]. There are two different varieties of CagA: Western and East Asian. CagA is built on an EPIYA (glutamineproline-isoleucine-tyrosine-alanine) repeating amino acid sequence at its 30 ends. When the T4SS injects this protein motif into cells, it gets phosphorylated.

   Whereas the East Asian EPIYA has an A-B-D sequence, the Western EPIYA motif has an A-B-C pattern where EPIYA-C can be repeated more than once [13].

3. Urease is the most frequently expressed protein by *H. pylori* and is one of the most important virulence factors involved in bacterial metabolism and colonization within the gastric mucosa. Both the intracellular compartment and the surface of *H. pylori* bacteria contain urease; hence, internal and external urease can be separated based on their location [14]. As urease is essential for bacterial colonization of the gastric mucosa, urease-negative mutants are unable to do so at physiological pH levels to the same extent as urease-positive *H. pylori* strains [15].

4. Flagellum: *H. pylori* flagellum is an essential component for permitting the chemotaxis and movement of bacteria. The precise number of flagella is related to the movement speed of *H. pylori* and may vary across species [16].

5. Catalase: one of the most highly expressed proteins in *H. pylori* strains isolated from the stomach mucosa, catalase levels are thought to range between 4 and 5% of the total protein composition of *H. pylori* [17]. Compared to catalase from other species, *H. pylori* catalase is more resistant to inhibition by cyanide or aminotriazole [18].

6. One of the *H. pylori* enzymes, superoxidase dismutase (SOD), shields the bacteria from reactive oxygen species (ROS), permitting the preservation of the appropriate homeostasis. SOD is exclusively found on the cell surface, unlike catalase. SOD speeds up the conversion of superoxide to oxygen, avoiding the production of too many harmful superoxide free radicals [19].

7. Lewis Antigens: majority of *H. pylori* strains exhibit at least one kind of Lewis (Le) antigen, which are fucosylated glycolipids that are a part of the *H. pylori* O-specific chain of the lipopolysaccharide (LPS). Le antigens are expressed on gastric epithelial cells, making Le antigen expression on bacterial cell surfaces one of the most efficient ways for *H. pylori* colonization of the stomach mucosa and provoking host immunological responses [20].

8. Phospholipases: *H. pylori* phospholipases destroy the mucus layer, the physiological activities of the gastric epithelial cells are gradually lost. In addition to causing mucosal injury, phospholipases encourage persistent inflammation, which may further contribute to the development of peptic ulcers. As a result, the stomach microenvironment can support more bacterial colonization and survival [21].

9. Outer Inflammatory Protein A Outer inflammatory protein A (OipA), a member of the OMPs family and a virulence factor for *H. pylori*, is encoded by the hopH gene, It may have an impact on the clinical outcome of infected individuals since it is closely related to the adherence, colonization, onset, and development of gastrointestinal illnesses caused by bacteria [22].

10. Duodenal Ulcer Promoting Gene (DupA) is the *H. pylori* virulence factor, and its pathogenicity is linked to both the risk of gastritis and the development of duodenal ulcers. Nevertheless, DupA expression is adversely correlated with the risk of GC [23].

11. *Helicobacter pylori* neutrophil-activating protein (HP-NAP): a key component of *H. pylori's* pathogenicity, which contributes to both human inflammation and bacterial defense. To promote their pro-oxidant and pro-inflammatory actions, neutrophils, monocytes, and mast cells are among the innate immune cells that HP-NAP activates. Moreover, this protein stimulates T-helper type 1 (Th1) and cytotoxic T lymphocyte (CTL) activity, providing evidence that HP-NAP might cause stomach inflammation by triggering adaptive immunological responses [24].

Treatment

In the lack of a reliable vaccination, treating chronic *H. pylori* infection has become the primary method for controlling the bacteria's population spread, curing gastric lesions in infected individuals, and preventing the development of stomach cancer in the future [25].

Primary antibiotic resistance in *H. pylori* has emerged quickly because to the lack of effective treatment options, widespread use of certain antibiotics in the general population (such as clarithromycin for respiratory infections), and the species' outstanding capacity for adaptability [26].

The development of alternative treatment methods includes the use of probiotics and prebiotics as adjuvants in the treatment of *H. pylori*, antimicrobial peptides as antibiotic substitutes, ingestible photodynamic therapy devices, micro- and nanoparticles used as drug delivery systems, vaccines, natural products, and phage therapy [27].

Conclusions

Gastric cancer has a complicated and multifaceted etiology that includes genetic and epigenetic variations, host-related factors, and environmental variables. The most significant risk factor in the pathogenesis of this neoplasia is *H. pylori* infection, which has been proven to call upon several known pathways (and possibly more that have yet to be found) to cause the start and progression of gastric cancer. And therefore, preventative techniques must be established in order to identify high-risk individuals and provide a customized therapy before the onset of precancerous lesions, in addition to efforts to discover and verify novel biomarkers and changes in people's lifestyle and dietary habits.

Ethical Approval

The study was approved by the Ethical Committee. It was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008.

Conflicts of Interest

The authors declare that he has no competing interests.

Funding

None

Study registration

Not required.

References

1. Ishaq S, Nunn L. Helicobacter pylori and gastric cancer: A state of the art review. Gastroenterol. Hepatol. Bed Bench 2015;8:S6–S14**.**
2. International Agency for Research on Cancer (IARC). Schistosomes, Liver Flukes and Helicobacter pylori; IARC: Lyon, France, 1994; pp. 1–241**.**
3. Machlowska J, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric Cancer: Epidemiology, Risk Factors, Classification, GenomicCharacteristics and Treatment Strategies. Int. J. Mol. Sci 2020; 21:4012**.**
4. Moyat M, Velin D. Immune responses to Helicobacter pylori infection. World journal of gastroenterology: WJG 2014; 20(19):5583**.**
5. Engler D B, Leonardi I, Hartung ML, Kyburz, A, Spath, S, Becher B, Müller A. Helicobacter pylori–specific protection against inflammatory bowel disease requires the NLRP3 inflammasome and IL-18. Inflammatory bowel diseases 2015; 21(4):854-861.
6. Aguilera-Correa J J, Urruzuno P, Barrio J, Martinez M J, Agudo S, Somodevilla A , Alarcón T. Detection of Helicobacter pylori and the genotypes of resistance to clarithromycin and the heterogeneous genotype to this antibiotic in biopsies obtained from symptomatic children. Diagnostic Microbiology and Infectious Disease 2017; 87(2):150-153**.**
7. Zandi F, Shirzad H, Bagheri N, et al. Helicobacter pylori and IL-23R gene polymorphism role in degeneration of gastric mucosa. American Journal of BioMedicine 2014;2(3):176-188.
8. Palframan SL, Kwok T, Gabriel K. Vacuolatingcytotoxin A (VacA), a key toxin for Helicobacter pylori pathogenesis. Front Cell Infect Microbiol 2012; 2:92.
9. González-Rivera C, Algood HMS, Radin et al. The intermediate region of Helicobacter pylori VacA is a determinant of toxin potency in a Jurkat T cell assay. Infection and immunity 2012; 80(8):2578-2588.
10. Yahiro K, Akazawa Y, Nakano M, et al. Helicobacter pylori VacA induces apoptosis by accumulation of connexin 43 in autophagic vesicles via a Rac1/ERK-dependent pathway. Cell Death Discov 2015; 1:1–15.

11. Covacci A, Censini S, Bugnoli M, et al. Molecular characterization of the 128-kDa immunodominant antigen of Helicobacter pylori associated with cytotoxicity and duodenal ulcer. ProcNatlAcadSci USA 1993; 90:5791–5.
12. Blaser MJ, Perez-Perez GI, Kleanthous H, et al. Infection with Helicobacter pylori strains possessing cagA is associated with an increased risk of developing adenocarcinoma of the stomach. Cancer Res 1995; 55:2111–5.
13. Higashi H, Tsutsumi R, Fujita A, et al. Biological activity of the Helicobacter pylori virulence factor CagA is determined by variation in the tyrosine phosphorylation sites. ProcNatlAcadSci USA 2002; 99:14428–33.
14. Kasahun G G , Demoz G. T, Desta D. M.Primary resistance pattern of Helicobacter pylori to antibiotics in adult population: a systematic review. Infect. Drug. Resistance 2020; 13:1567–1573.
15. Nolan KJ, Mcgee DJ, Mitchell HM, et al. In Vivo Behavior of a Helicobacter pylori SS1 nixA Mutant with Reduced Urease Activity. Infect. Immun 2002; 70:685–691.
16. Martínez L E, Hardcastle J M, Wang J, et al. Helicobacter pylori strains vary cell shape and flagellum number to maintain robust motility in viscous environments. Mol. Microbiol 2015; 99:88–110.
17. Mahawar M, Tran V, Sharp JS, Maier RJ. Synergistic roles of Helicobacter pylori methionine sulfoxidereductase and GroEL in repairing oxidant-damaged catalase. J. Biol. Chem 2011; 286:19159–19169.
18. Switala J, Loewen P.C. Diversity of properties among catalases. Arch. Biochem. Biophys. 2002; 401:145–154.
19. Baj J, Forma A., Sitarz M, Portincasa P, Garruti G, Krasowska D, Maciejewski R. Helicobacter pylori virulence factors-mechanisms of bacterial pathogenicity in the gastric microenvironment. Cells, 2020; 10(1): 27.
20. Lee H S, Choe G, Kim W H, Kim H H, Song J, Park KU. Expression of Lewis antigens and their precursors in gastric mucosa: Relationship with Helicobacter pylori infection and gastric carcinogenesis. J. Pathol 2006; 209:88–94.
21. Lusini P, Figura N, Valassina M, et al. Increased phospholipase activity in Helicobacter pylori strains isolated from patients with gastric carcinoma. Dig. Liver Dis 2005; 37:232–239.
22. Zhang J, Qian J, Zhang X, Zou Q. Outer membrane inflammatory protein A, a new virulence factor involved in the pathogenesis of Helicobacter pylori. Mol. Biol. Rep 2014; 41:7807–7814.
23. Imagawa S, Ito M, Yoshihara M, Eguchi H, Tanaka S, Chayama K. Helicobacter pylori dupA and gastric acid secretion are negatively associated with gastric cancer development. J Med Microbiol 2010; 59 Pt 12:1484–1489.
24. Fu H W, Lai YC. The Role of Helicobacter pylori Neutrophil-Activating Protein in the Pathogenesis of H. pylori and Beyond: From a Virulence Factor to Therapeutic Targets and Therapeutic Agents. International Journal of Molecular Sciences 2023; 24(1):91.

25. Yamaoka Y. How to eliminate gastric cancer-relateddeath worldwide. Nat. Rev. Clin. Oncol 2018; 15:407–408.
26. Scott D R, Weeks D, Hong C, Pontius S, Melchers K, Sachs G. The role of internal urease in acid resistance of Helicobacter pylori. Gastroenterology 1998; 114:58–70.
27. Sousa C, Ferreira R, Azevedo N F, Oleastro M, Azeredo J, Figueiredo C, Melo L D. Helicobacter pylori infection: From standard to alternative treatment strategies. Critical reviews in microbiology 2022; 48(3):376-396.