ASJMS
Al-Salam Journal for Medical Sciences
Journal Homepage: http://journal.alsalam.edu.iq/index.php/ajbms
e-ISSN: 2959-5398, p-ISSN: 2958-0870

A An Updated Evaluation of the Link Between Helicobacter pylori and Colorectal cancer

Ayat Majeed Zeadan [1, 2]*, Tarek A.A. Mousaa [2] and Ahmed Rushdi Abdullah[1]

[1]Microbiology Department, Collage of Medicine, Al-Iraqia University, Baghdad, 10011, Iraq

[2]Botany and Microbiology Department, Faculty of science, Cairo University, Cairo, 11311, Egypt

*Corresponding Author: Ayat Majeed Zeadan

DOI: https://doi.org/10.55145/ajbms.2026.05.01.014
Received December 2025; Accepted January 2026; Available online Febuary 2026

ABSTRACT: The Gram-negative bacterium Helicobacter pylori (H. pylori) is linked to gastric disorders such as gastritis, peptic ulcers, and stomach cancer. There may be a link between H. pylori infection and the risk of extra gastric illnesses, such as colorectal cancer, according to new research. the current knowledge of the virulence factors and the relationship between H. pylori infection and colorectal cancer. Studies indicate that H. pylori infection may affect colorectal carcinogenesis by indirect effects on systemic inflammation, hormonal changes, or direct effects via bacterial translocation, while the precise mechanisms behind this link remain unclear. Some epidemiological studies have reported a positive association between H. pylori infection and the risk of colorectal cancer or adenomas, although results are inconsistent. Further research is needed to clarify the nature of this association, understand the underlying mechanisms, and determine the potential implications for colorectal cancer prevention and management.

Keywords: H. pylori, cancer, virulence factors, epidemiology, oncology

1. INTRODUCTION TO COLORECTAL CANCER

The most prevalent type of gastrointestinal cancer is colorectal cancer. According to studies based on clinical trials, certain colorectal cancer screening tests are very helpful in identifying the disease early on, which lowers the number of fatalities from it. Faecal occult blood test, colonoscopy, sigmoidoscopy, DNA stool test, and virtual colonoscopy are the top five colorectal cancer screening tests 1–4.

Mucosal epithelial cell proliferation that is not cancerous is typically the first sign of colorectal cancer (CRC). These growths are called polyps, and they can grow slowly for ten to twenty years before developing into cancer 5.

Cancers localized in nature have penetrated the wall but not broken through. Cancers that have spread to neighboring lymph nodes or tissues are called regional cancers. On the other hand, cancers that have spread to distant organs with capillary beds—like the liver or lungs—may be classified as distant cancers 6.

Intestinal inflammation and altered gut microbiota to stimulate an immune response are two consequences of specific dietary and lifestyle choices that can accelerate the growth of polyps and their transformation into cancer. Similarly, oncogenes and tumour-suppressor genes can undergo spontaneous or hereditary. The prevention of CRC may be achieved through genetic testing, lifestyle modification, and early screening 7,8.

1.1 Epidemiology

According to the GLOBOCAN estimates CRC was the second leading cause of cancer-related death globally (after lung cancer) in 2020 9-11. The overall CRC incidence proportion (CIP) for both genders rose by 5.11% annually, from 2.28 to 6.18 per 100,000 people in 2000 and 2019, respectively. Patients aged 20 to under 50 had an increased

incidence proportion (IP) of CRC from 1.46 in 2000 to 4.36 per 100,000 people in 2019, representing an annual percentage change of 5.6%. In 2000 and 2019, the IP and APC for patients over 50 increased from 12.7 to 40.59 per 100,000 population, from 3.69% in 2000 to 6.5% in 2019, and the proportion of CRC cases to all malignancies in Iraq increased. In 2010 and 2019, CRC deaths increased from 1.25 to 1.77 per 100,000 populations, indicating an APC of 3.54%. In terms of anatomy, colon (C18) tumours accounted for 59.2% and 65.7% of cases in 2000 and 2019, respectively. Rectosigmoid junction tumors (C19), which were 3.6% in 2000 but only 2% in 2019, were like rectal (C20) tumors, which were 37.2% in 2000 and dropped to 31.4% in 2019 12.

1.2 ETIOLOGY OF COLON CANCER

Multiple tumorigenic pathways can lead to colorectal cancer, a heterogeneous disease. The "adenoma-carcinoma sequence" process leads to the development of colon and rectal adenocarcinomas. This process gradually transitions from normal tissue to dysplastic epithelium to carcinoma 13.Although the etiology of CRC is unknown, the following factors may be involved: Genetic factors14 and Dietary factors 15.Colonic polyps cause precancerous stages that last two to five years, and about 15 to 40 percent of colon cancers start from these 16.

Other elements Patients undergoing pelvic radiation therapy have a higher incidence of sigmoid and rectal cancer. Recessive motion and other lifestyle factors, such as being overweight, are risk factors for colorectal cancer 17, figure 1.

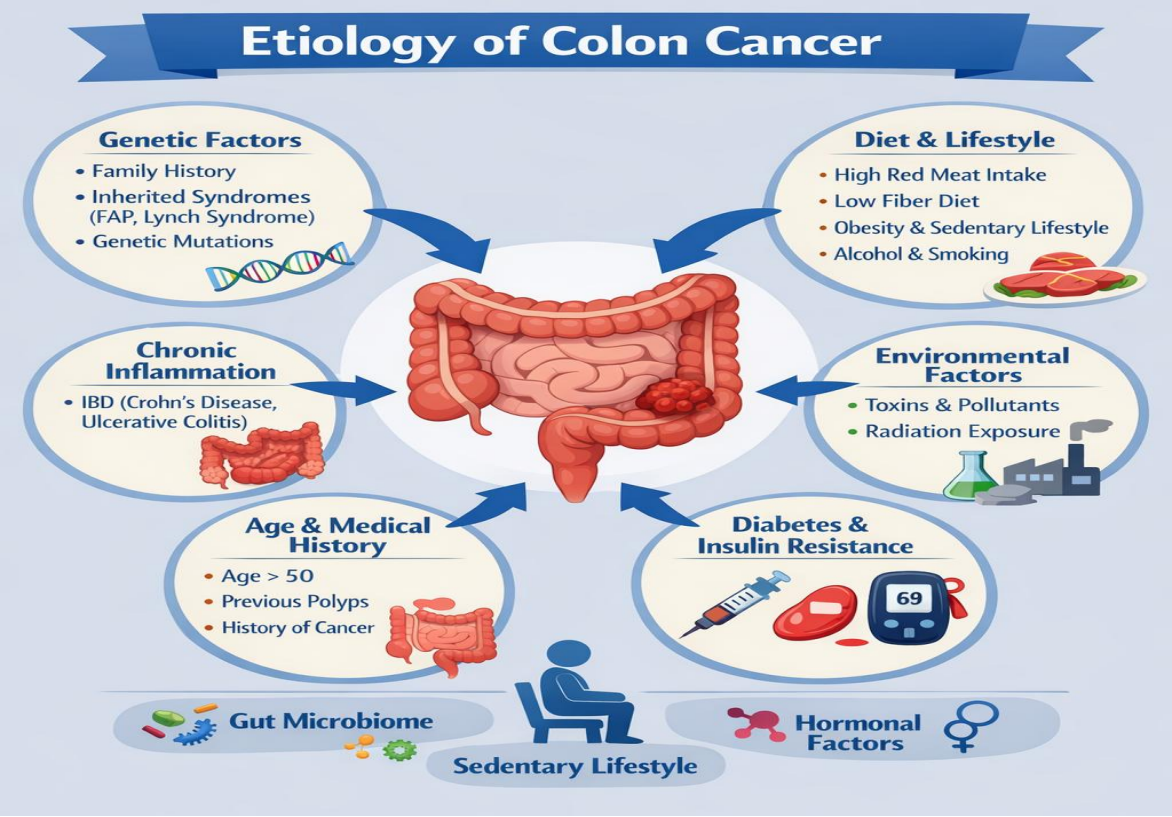

FIGURE 1. - Etiology of colon cancer 13

1.2.1 CLASSIFICATION OF COLON CANCER

Adenocarcinoma, the most prevalent subtype, makes for 85% of CRC cases globally and is not otherwise identified. Mucinous carcinoma, which makes up 5–20% of CRC cases globally 18. Mucinous carcinoma used to be invariably linked to a poor prognosis, but this appears to be changing 19,20. The incidence of medullary carcinoma has been estimated to be 4%, and its identification has increased recently 21. Solid growth combined with an inflammatory response is what defines this subtype. Patients with medullary carcinomas have a great prognosis, and the tumours are virtually always microsatellite unstable, most often in conjunction with BRAF mutations 22-24.

CRC can also be categorized based on where it is found. Because of the differences in treatment choices, colon cancer and rectal cancer have long been distinguished from one another. More recently, however, there has been increased attention in this distinction due to the variety of potential screening methods. However, considering the variations in biology and behavior, the division of colon cancer by embryological origin (midgut or proximal colon and hindgut or distal colon) also appears to be significant for results 25,26. Most tumors exhibiting microsatellite instability demonstrate hypermethylation of hMLH1, predominantly observed in the proximal colon of elderly women 27,28.

1.2.2 GENES INDUCES COLON CANCER

The RAS and RAF family proteins participate in cell survival and proliferation by mediating growth factor receptor signaling. Overactivity of these signaling pathways is frequently observed in a variety of cancers. RAS and BRAF gene mutations are the primary causes of it. Women are more likely to have right-sided colon cancer, which also typically exhibits BRAF mutations and microsatellite instability. Men are more likely to develop left-sided colon cancer, which also exhibits KRAS mutations and chromosomal instability 29-37.

KRAS and BRAF mutations in colorectal cancer (CRC) are characterized as mutually exclusive, suggesting functional redundancy or incompatibility, resulting in the elimination of cells harboring both mutations36,38.

Collagen and elastin (ELN) are fibrous proteins that confer structural integrity and functionality to tissues. Elevated levels of this protein have been noted in many fibrotic illnesses, encompassing renal, pulmonary, and hepatic fibrosis. Research indicates that fibrosis has a role in cancer progression and in the initial phases of CRC 39-42.

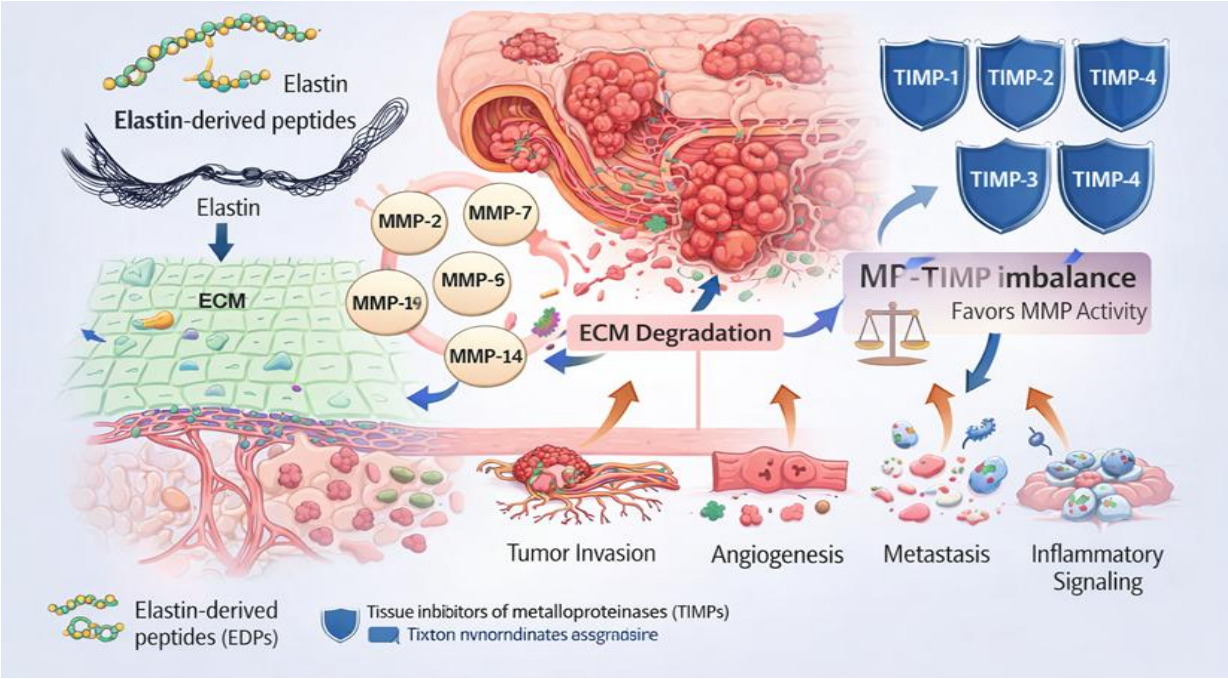

FIGURE2. - Role of Elastin and metalloproteinases (TIMPs) in Colon Cancer

The evidence indicates that the overexpression of TIMP3 is a logical multi-phenotypic strategy for cancer therapy. Adenoviral-mediated TIMP3 overexpression diminished blood vessel density, enhanced apoptosis, and markedly inhibited tumor growth in an in vivo melanoma model, while also suppressing malignant behaviors including migration, invasion, and tumor formation in CRC cells. Consequently, TIMP3 may serve as a viable target for cancer therapy, offering multiple therapeutic advantages 43.

2. HELICOBACTER PYLORI

Helicobacter pylori infection impacts around fifty percent of the global population which alters the stomach mucosa in a number of ways, resulting in the epithelium's neoplastic transformation. As a result, H. pylori infection triggers a variety of immunological reactions that are directed against H. pylori and are managed by the bacteria itself 44–46. H. pylori's helical form makes it easier for the bacteria to move around efficiently. On the other hand, the coccoid form makes it easier for the bacteria to colonize the mucus layer of the stomach epithelium, increasing its invasiveness. Additionally, H. pylori can form biofilms to lessen its susceptibility to some medications, which can lead to alterations that increase drug resistance and make efforts to eradicate the bug more difficult 47-51. H. pylori's adaptation processes include both environmental and bacterial factors that let it survive in the stomach milieu, where acidity levels are lower than 3.0 47-59.

2.1 CLASSIFICATION

With H. pylori serving as the type species, the genus Helicobacter was established in 1989. About eighteen species now make up the genus. Although some Campylobacter species were reclassified, most of the microorganisms were found in the stomach or intestines of mammals that served as hosts. Sheathed flagella are a fundamental characteristic

shared by nearly all heliobacteria. Most species, especially those linked to the gastric mucosa, have a strong ureolytic potential and show significant variation in cell morphology, including length, the number and location of flagella, and the presence of periplasmic fibrils 60.

This bacterium is classified as one of the epsilon-proteobacteria group, including other pathogenic bacteria such as Campylobacter and Wolinella. The classification of H. pylori is based on its unique morphology, biochemistry, and genetic characteristics 61,62.

Phylogenetic analysis of H. pylori has revealed that it is a diverse species with multiple strains and subpopulations 63. Based on their geographic origin, H. pylori strains can be divided into separate populations, each of which is found in a different region of the world 64. For instance, strains of H. pylori from Europe and Africa differ from those from East Asia. This categorization has significant ramifications for comprehending the pathophysiology and epidemiology of H. pylori infections. 65-68.

2.2 VIRULENCE FACTOR

The virulence factors of H. pylori modulate and regulate of immune responses perpetuating chronic inflammation 47, table 1.

Table 1. - Virulence factors 47

Virulence Factor	Function
Urease	Protects from gastric acidity Facilitates bacterial colonization Stimulates bacterial nutrition Generates the proton motive force Regulates host immunological responses (promoted apoptosis, chemotaxis of neutrophils and monocytes, modified opsonization, increased secretion of pro-inflammatory cytokines) Stimulates platelet activation Stimulates angiogenesis
Flagellum	Enhances bacterial motility Stimulates chemotaxis Takes part in the biofilm formation Facilitates inflammation and immune evasion
Cytotoxin-associated gene A	Stimulates inflammatory responses

Vacuolating cytotoxin A	Involved in the formation of pores Promotes the autophagy pathways Forms the intracellular vacuoles and impaired autophagosomes Induces apoptosis and necrosis Inhibits the activity and proliferation of T and B cells Inhibits the IFN-β signaling, inducing macrophage apoptosis Induces the release of IL-8 Differentiation of the regulatory T cells into effector T cells Prevents cellular elongation by inhibiting the Erk1/2 kinase pathways
Catalase	Induces mutagenesis Facilitates inflammation Protects *H. pylori* from complement-mediated killing Maintains bacterial survival at the cell surface of the phagocytes and in the macrophage phagosomes Protects *H. pylori* from phagocytosis
Superoxidase dismutase	Facilitates bacterial colonization Protects from ROS Inhibits the production of pro-inflammatory cytokines Stimulates the activation of the macrophages

Lewis antigens	**Protects *H. pylori* from the host defense mechanisms** **Enhances bacterial survival** **Enhances the adhesive properties and further internalization**
Arginase	Stimulates apoptosis Prevents bacterial killing Provides acid resistance in the gastric microenvironment Inhibits the proliferation of T cells Inhibits the production of NO Impairs the host's immune responses Induces the apoptosis of macrophages Impairs Th1/Th17 differentiation
Phospholipases	Degradation of various lipids Damage the mucus layer. Stimulate chronic inflammation Facilitate bacterial colonization and survival. Activate the ERK1/2 signaling pathway
Lipopolysaccharide	Induces the host's inflammatory responses by molecular mimicry Protects the bacterium from potentially toxic compounds

Blood group antigen-binding adhesin	**Enables bacterial adherence to gastric epithelial cells** **Stimulates the delivery of toxins (due to the increased T4SS activity)** **Stimulates the inflammatory responses (excessive IL-8 release, granulocyte infiltration)**
Sialic acid-binding adhesin	Stimulates neutrophil activation and infiltration Facilitates bacterial colonization Induces oxidative damage
Outer inflammatory protein A	Activates the apoptotic cascade Promotes the secretion of the pro-inflammatory cytokines such as IL-1, IL-6, IL-8, IL-11 IL-17, matrix metalloproteinase 1 (MMP-1), TNF-α, RANTES Regulates β-catenin levels Inhibits the maturation of dendritic cells Takes part in CagA delivery into the host cells Increases microRNA-30b levels
Duodenal ulcer-promoting gene A	Involved in the formation of T4SS Stimulates the infiltration of the inflammatory cells Facilitates urease and IL-8 secretion and IL-12 release from the monocytes Activates the mitochondria-mediated apoptotic pathways Facilitates bacterial tolerance in the acidic microenvironment

Adherence-associated lipoproteins A and B	**Enables bacterial adherence to gastric epithelial cells** **Stimulates bacterial colonization** **Takes part in the formation of the biofilm** **Induces the release of pro-inflammatory factors (IL-6 and IL-8)**
LacdiNAc-specific adhesin	Facilitates adherence to gastric epithelial cells
***Helicobacter pylori* outer membrane protein Q**	Facilitates adherence to gastric epithelial cells Enables bacterial survival in the acidic gastric microenvironment Stimulates the infiltration of pro-inflammatory factors Facilitates T4SS activity Enables the survival of neutrophils Inhibits the natural killer and T cells' functions
***Helicobacter pylori* outer membrane protein Z**	Facilitates adherence to gastric epithelial cells Disturbs gastric acid secretion
Induced by contact with epithelium gene A	Induces oxidative DNA damage Stimulates the release of pro-inflammatory factors (IL-8, IL-1) Facilitates granulocytic and lymphocytic infiltrations
Cholesteryl α-glucosyltransferase	Prevents *H. pylori* from being phagocytosed and immune responses Regulates the responses from the $CD4^+$ T-cells, IL-4, and IFN-γ pathways Stimulates the secretion of IL-8 Crucial for proper bacterial growth, survival, and antibiotic resistance Interrupts the autophagosome-lysosome fusion
γ-glutamyl-transpeptidase	Induces the release of ROS Inhibits cellular proliferation Facilitates apoptosis and necrosis Incudes the release of IL-8, IL-10, COX-2, inducible iNOS, caspase-3 and -9 Inhibits CD4+ T cell proliferation and stimulates CD8+ T cell infiltration Prevents the differentiation of the dendritic cells Stimulates DNA damage Reduces cell viability
Neutrophil-activating protein	Facilitates neutrophil adherence to gastric epithelial cells Produces ROS and myeloperoxidase Activates neutrophils and mast cells, and the migration of monocytes Stimulates the infiltration of monocytes and polymorphonuclear granulocytes Stimulates the release of IL-8, MIP-1α, MIP-1β, TNF-α, IL-6, β-hexosaminidase Impairs the epithelial tight junctions and basal membranes Facilitates *H. pylori* growth
High temperature requirement A	Impairs the functions of the epithelial barrier by disrupting adherens junctions, tight junctions, and extracellular matrix proteins Facilitates *H. pylori* migration properties

Heat shock proteins	**Maintains the proper structural and functional properties of the cellular proteins**
	Protects from oxidative stress
	Regulates apoptosis and autophagy
	Crucial for proper urease activation
	Induces the release of COX-2, IL-8, TNF-α, MMP3, and MMP7
	Facilitates adherence to gastric epithelial cells
	Facilitates tumor cell migrations
	Enhances angiogenesis

The details of virulence variables, which encompass 69:

2.2.1 UREASE

This is the most abundant protein that H. pylori produces, and it is an essential component of its virulence that plays a major role in the bacterial metabolism and colonization of the gastric mucosa. Because H. pylori urease is found on the bacterial surface as well as in the bacterial cytoplasmic compartment, two types of urease can be distinguished according to where they are found: internal and external70. When the pH of the mucus rises above 8, H. pylori colonization may stop; this process is probably triggered to prevent excessive bacterial growth in the stomach mucus 47.

Urease is a crucial enzyme that promotes bacterial colonization in the stomach mucosa, protects the bacteria from gastric acidity by increasing the production of ammonia, facilitates bacterial nutrition by releasing host metabolites, and produces proton motive force during urea hydrolysis 71,72. Through a number of mechanisms, including altered opsonization, increased neutrophil and monocyte chemotaxis, apoptosis promotion. It is believed that urease stimulates angiogenesis, which leads to increased GC development 73, 74.

2.2.2 FLAGELLUM

This crucial element has a major impact on bacterial motility and chemotaxis. Each of H. pylori's two to six sheathed unipolar flagella, which are about three micrometers long, are shielded from the acidic gastrointestinal environment by their sheaths. The exact number of flagella is correlated with the H. pylori locomotion velocity, which can differ between species. 75.

The flagellum, a determinant of bacterial movement, facilitates colonization of the gastric mucosa; thus, it represents a critical virulence factor linked to H. pylori pathogenicity, particularly during the initial phases of bacterial invasion. It was shown that a reduced number of motile strains of H. pylori complicates subsequent colonization of the gastric mucosa 76, Which contribute to H. pylori-induced inflammation and immunological evasion; moreover, they play a role in biofilm development 77.

2.2.3. CYTOTOXIN-ASSOCIATED GENE A

H. pylori strains can be classified into two primary subtypes: CagA-positive and CagA-negative strains. CagA is delivered into the cell through the pilus created by T4SS, resulting in cellular modifications that hinder motility, proliferation, and apoptosis, while also reorganizing the entire cytoskeleton. The attachment of H. pylori to stomach epithelial cells stimulates the expression of cagA 78. The presence of CagA is typically linked to an increased prevalence of inflammatory responses and enhanced damage to the stomach mucosa. CagA-positive H. pylori strains induce an increase in IL-8 and IL-12 levels in the serum of infected patients 79.

CagA-positive strains exhibit more motility than CagA-negative strains, suggesting that CagA is linked to bacterial motility 80. The CagA gene exhibits several variations, and a correlation exists between specific cagA genotypes and the ethnicity of patients 81. CagA exhibits antiapoptotic properties, enhances motility, and promotes host cell proliferation and expansion. CagA is strongly linked to the initiation and subsequent advancement of epithelial-mesenchymal transition (EMT) in the gastric mucosa, correlating with enhanced invasive characteristics 82, 83.

CagA-positive bacterial infection promotes the development of duodenal ulcers, gastric carcinogenesis, and active or atrophic gastritis. VacA, OipA, and CagA significantly increases inflammatory responses, worsening patient clinical outcomes and raising the risk of increased gastrointestinal disease incidence84.

2.2.4. VACUOLATING CYTOTOXIN A

is a cytotoxin that facilitates pore development, with its modes of action and ultimate pathogenicity85. VacA is a major virulence factor facilitating bacterial colonization and persistence in the gastric epithelium84. Currently, multiple VacA genotypes have been identified, including s1, s2, m1, m2, s1m1, s1m2, s2m2, and s2m1. The VacA s1 genotype is prevalent among H. pylori-infected individuals, and a correlation exists between this genotype and peptic ulcer illness 47, 86-88, figure 3.

2.3 OTHER VIRULENCE FACTORS IN H. PYLORI

2.3.1 ENZYMES

Catalase constitutes around 4–5% of the total protein composition in H. pylori, playing a crucial role in safeguarding the bacterium against oxidants and oxidative stress, hence enhancing its survival within macrophage phagosomes and offering protection against phagocytosis; it also participates in the control of immunological responses 89.

Superoxide dismutase (SOD) this enzyme shields the bacterium from reactive oxygen species (ROS) and helps maintain cellular homeostasis only on the cell surface. Based on its properties and chemical composition, superoxide dismutase (SOD), a metalloenzyme, can be divided into three isoforms, including copper-zinc SOD. Mn-SOD expression is higher in H. pylori-infected individuals with moderate to severe gastric mucosal inflammation than in those with intact gastric mucosa 47. Instead of the corpus, Mn-SOD expression was primarily increased in the pit cells of the antrum90.

The arginase of H. pylori is essential for bacterial colonization as it confers acid tolerance inside the gastric milieu. H. pylori arginase demonstrates enhanced catalytic activity with Co^{2+} or Ni^{2+} as cofactors compared to Mn^{2+} and exhibits superior activity at acidic pH rather than alkaline pH, with optimal performance at pH 6.1 47. Arginase decreases nitric oxide generation, hence compromising the bactericidal efficacy of macrophages 91, 92. In addition to γ-glutamyl-transpeptidase (GGT) 93-95.

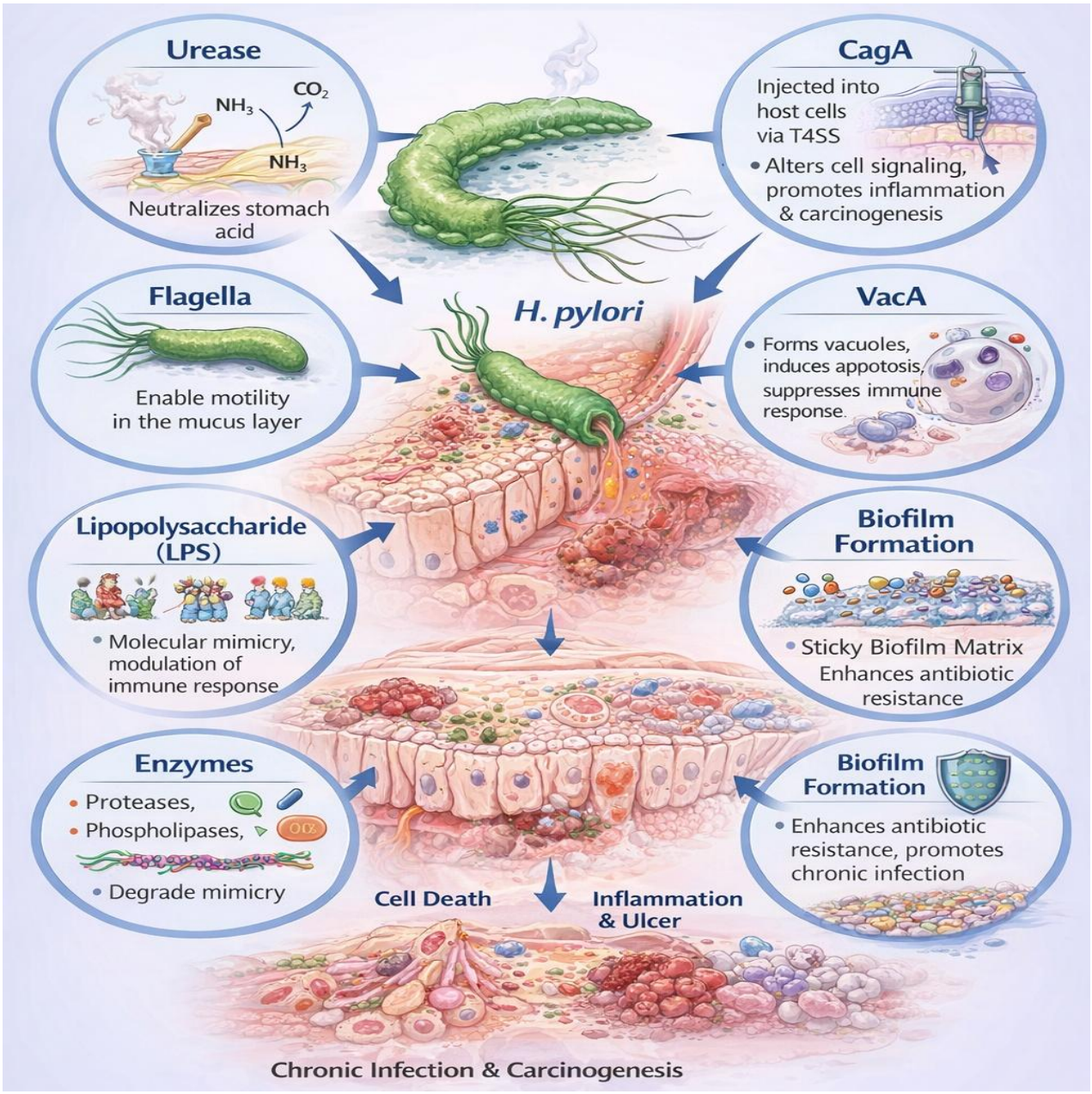

FIGURE 3. - Virulence factors of H. pylori

2.3.2 LIPOPOLYSACCHARIDE (LPS)

Serves as a critical virulence factor, facilitating the initiation and advancement of a chronic bacterial infection 96. In addition to TLR4, LPS activates TLR-2 on the cellular membrane, prompting the NFκB-dependent production of claudins -4, -6, -7, and -9, and amplifying Th1 immune responses through the release of these inflammatory mediators97.

LPS facilitates the prolonged persistence of H. pylori, which markedly induces host inflammatory responses 98. LPS facilitates the production of substantial quantities of several interleukins and immunological mediators99,100.

2.3.3. BLOOD GROUP ANTIGEN-BINDING ADHESIN (BABA)

Expression of this protein may serve as a biomarker for H. pylori infection 79, that significantly correlated with the presence of cagA in specific H. pylori strains 101. BabA, CagA, and VacA exhibit a synergistic effect, exacerbating the severity and clinical outcomes in patients with gastritis. In addition to bacterial adhesion and colonization, BabA induces many immunological responses, including granulocyte infiltration and IL-8 production, hence exacerbating gastric inflammation 102, 103. BabA can bind to its receptors in both the oral mucosa and stomach mucosa 79,104.

Other virulence component include

Sialic acid-binding adhesin (SabA)105,106, Outer inflammatory protein A (OipA) 107-111, Induced by contact with epithelium gene A (IceA)112, and Neutrophil-activating protein (NAP) 113, 114.

3. Heat shock proteins (Hsps)

are molecular chaperones that are necessary for bacteria, including H. pylori, to survive and adapt. Heat shock proteins (HSPs) are essential for H. pylori to cope with environmental stressors such as temperature fluctuations, oxidative stress, and the acidic conditions of the human stomach. They control immunology, inflammation, carcinogenesis, autophagy, apoptosis, and oxidative stress defense. 115.

Numerous heat shock proteins (HSPs) are produced by H. pylori, including Hsp70-HspA, which is necessary for the proper activation of urease during H. pylori infection, and HspA (Hsp10) and HspB (Hsp60), which are homologous to GroES and GroEL, respectively. HspA may be a good molecular target for anti-ulcer medications because it binds to nickel and bismuth ions. These proteins aid in the refolding of denatured proteins, participate in protein folding, and prevent protein aggregation 116.

By assisting the bacterium in adapting to the stomach environment and avoiding host immune responses, HSPs in H. pylori may play a role in the pathophysiology of gastric disorders. HSPs in H. pylori may be targets for therapeutic interventions or the development of a vaccine against H. pylori infections due to their significance in bacterial survival and stress response. Novel approaches to managing H. pylori-related illnesses may be revealed by more investigation into the precise functions of HSPs in H. pylori pathogenesis and their interactions with the host. 116,117.

3. H. Pylori and cancer

H. pylori promotes several changes in the stomach mucosa, leading to neoplastic transformation of the epithelium. Consequently, H. pylori infection initiates a complex array of immune responses, aimed against H. pylori and managed by the bacterium itself, originating from activation in the Peyer's patches and the mesenteric lymph nodes of the small intestine 118. The principal pro-inflammatory response to H. pylori is a combined T helper (Th)1 and Th17 response. This pertains primarily to the existence and function of a type 4 secretion system, which facilitates the translocation of the oncogenic and highly immunogenic protein CagA into gastric epithelial cells 119,120, figure 4.

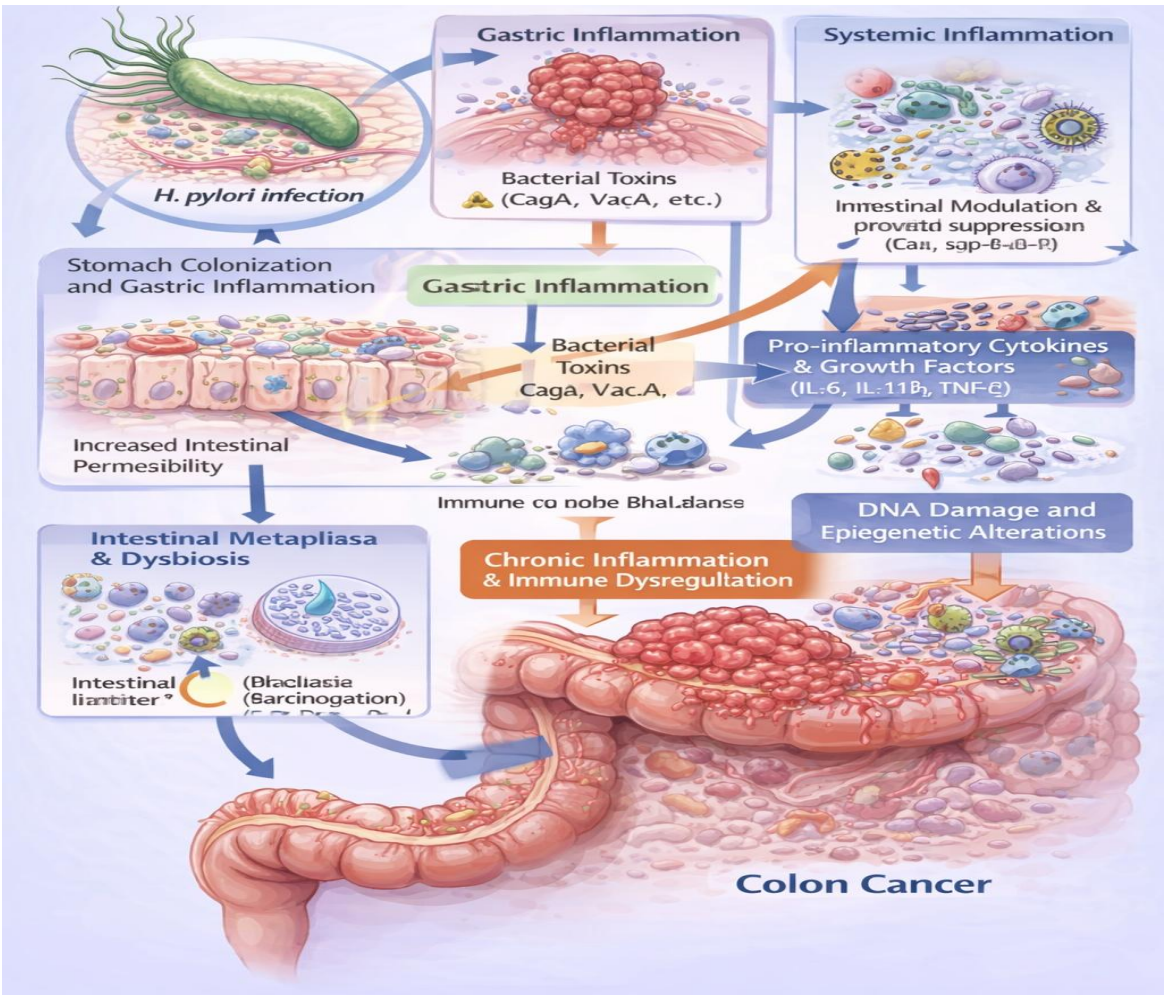

FIGURE 4. - development of cancer

Despite H. pylori infection being confined to the stomach, increasing epidemiological evidence suggests a correlation between H. pylori infection and many extra gastric illnesses. A heightened risk of colorectal cancer (CRC) has been documented in association with H. pylori infection status 121.

3. CONCLUSION

Although some evidence points to a possible link between H. pylori infection and colorectal cancer, the relationship is still unknown and needs more research. The mechanisms by which H. pylori may affect colorectal carcinogenesis are poorly understood, and the available data are conflicting. Further research is necessary to elucidate this association given the high global prevalence of H. pylori infection and the importance of colorectal cancer as a public health concern. Comprehending the possible connection between H. pylori and colorectal cancer may have consequences for colorectal cancer screening, prevention, and treatment approaches in relation to H. pylori infection.

Funding

None

ACKNOWLEDGEMENT

This study is full funded by author.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

REFERENCES

[1] J. J. Granados-Romero et al., “Colorectal cancer: A review,” Int. J. Res. Med. Sci., vol. 5, p. 4667, 2017.
[2] H. S. Q. Alhilfi et al., “Colorectal cancer epidemiology and clinical study in Misan,” J. Coloproctology, vol. 39, pp. 159–162, 2019.
[3] M. Aljarshawi et al., “Misleading presentation of colorectal cancer in an otherwise healthy patient,” J. Fac. Med. Baghdad, vol. 62, pp. 132–138, 2020.
[4] N. K. Dhahir and A. A. Noaman, “A comparative study of colorectal cancer based on patient’s age,” J. Fac. Med. Baghdad, vol. 63, pp. 70–73, 2021.
[5] M. B. Huck and J. L. Bohl, “Colonic polyps: Diagnosis and surveillance,” Clin. Colon Rectal Surg., vol. 29, pp. 296–305, 2016.
[6] P. Rawla, T. Sunkara, and A. Barsouk, “Epidemiology of colorectal cancer: Incidence, mortality, survival, and risk factors,” Gastroenterol. Rev., vol. 14, pp. 89–103, 2019.
[7] J. Kim and H. K. Lee, “Potential role of the gut microbiome in colorectal cancer progression,” Front. Immunol., vol. 12, Art. no. 807648, 2022.
[8] H. Pandey et al., “Gut microbiota in colorectal cancer: Biological role and therapeutic opportunities,” Cancers, vol. 15, Art. no. 866, 2023.
[9] G. Roshandel, F. Ghasemi-Kebria, and R. Malekzadeh, “Colorectal cancer: Epidemiology, risk factors, and prevention,” Cancers, vol. 16, Art. no. 1530, 2024.
[10] H. Sung et al., “Global cancer statistics 2020,” CA Cancer J. Clin., vol. 71, pp. 209–249, 2021.
[11] R. Marcellinaro et al., “Colorectal cancer: Current updates and future perspectives,” J. Clin. Med., vol. 13, Art. no. 40, 2023, doi: 10.3390/jcm13010040.
[12] S. Ibrahem, H. Ahmed, and S. Zangana, “Trends in colorectal cancer in Iraq over two decades,” Ann. Saudi Med., vol. 42, pp. 252–261, 2022.
[13] G. Rindi et al., “Nomenclature and classification of neuroendocrine neoplasms,” in WHO Classification of Tumours of the Digestive System, 2010.
[14] M. Maida et al., “Screening of colorectal cancer: Present and future,” Expert Rev. Anticancer Ther., vol. 17, pp. 1131–1146, 2017.
[15] N. Murphy et al., “Lifestyle and dietary environmental factors in colorectal cancer susceptibility,” Mol. Aspects Med., vol. 69, pp. 2–9, 2019.
[16] L. Roncucci and F. Mariani, “Prevention of colorectal cancer,” Eur. J. Intern. Med., vol. 26, pp. 752–756, 2015.
[17] N. Imanbayev et al., “Tumor parenchymal and stromal ratios in colorectal cancer,” J. Fam. Reprod. Health, vol. 18, pp. 1–8, 2024.
[18] I. D. Nagtegaal et al., “The 2019 WHO classification of tumours of the digestive system,” Histopathology, vol. 76, pp. 182–188, 2020.

[19] N. Hugen et al., “Insight into mucinous colorectal carcinoma,” Ann. Surg. Oncol., vol. 21, pp. 2963–2970, 2014.
[20] N. Hugen et al., “Advances in the care of mucinous colorectal cancer,” Nat. Rev. Clin. Oncol., vol. 13, pp. 361–369, 2016.
[21] I. D. Nagtegaal and N. Hugen, “Tumour histology and oncological outcomes,” Curr. Colorectal Cancer Rep., vol. 11, pp. 259–266, 2015.
[22] J. Shia et al., “Morphological characterization of colorectal cancers in TCGA,” Mod. Pathol., vol. 30, pp. 599–609, 2017.
[23] A. Puccini et al., “Molecular profiling of signet-ring-cell carcinoma,” Oncogene, vol. 41, pp. 3455–3460, 2022.
[24] N. Hugen et al., “Colorectal signet-ring cell carcinoma,” Int. J. Cancer, vol. 136, pp. 333–339, 2015.
[25] F. Petrelli et al., “Left-sided vs right-sided colon cancer,” JAMA Oncol., vol. 3, pp. 211–219, 2017.
[26] X. Li et al., “MLH1 promoter methylation frequency in colorectal cancer patients and related clinicopathological features,” PLoS One, vol. 8, Art. no. e59064, 2013.
[27] S. M. Alzahrani, H. A. Al Doghaither, and A. B. Al-Ghafari, “General insight into cancer: An overview of colorectal cancer,” Mol. Clin. Oncol., vol. 15, Art. no. 271, 2021.
[28] J. Guinney et al., “The consensus molecular subtypes of colorectal cancer,” Nat. Med., vol. 21, pp. 1350–1356, 2015.
[29] S.-E. Kim et al., “Sex- and gender-specific disparities in colorectal cancer risk,” World J. Gastroenterol., vol. 21, pp. 5167–5175, 2015.
[30] A. B. Benson III et al., “Colon cancer, version 1.2017, NCCN clinical practice guidelines,” J. Natl. Compr. Canc. Netw., vol. 15, pp. 370–398, 2017.
[31] R. Moretto et al., “Location of primary tumor and benefit from anti-EGFR monoclonal antibodies,” Oncologist, vol. 21, pp. 988–994, 2016.
[32] L. Huang et al., “KRAS mutation: From undruggable to druggable,” Signal Transduct. Target Ther., vol. 6, Art. no. 386, 2021.
[33] M. Dillon et al., “Progress on Ras/MAPK signaling research,” Cancers, vol. 13, Art. no. 5059, 2021, doi: 10.3390/cancers13205059.
[34] M. Takeda et al., “The role of KRAS mutations in colorectal cancer,” Cancers, vol. 17, Art. no. 428, 2025, doi: 10.3390/cancers17030428.
[35] M. Meng et al., “Impact of KRAS on colorectal cancer,” Biomed. Pharmacother., vol. 140, Art. no. 111717, 2021.
[36] N. Garcia-Carbonero et al., “KRAS and BRAF mutations as biomarkers,” Cells, vol. 9, Art. no. 219, 2020, doi: 10.3390/cells9010219.
[37] K. S. Shan et al., “Targeting the BRAF/MAPK pathway across cancers,” Int. J. Mol. Sci., vol. 25, Art. no. 124, 2024.
[38] R. M. Guerrero et al., “Targeting BRAF V600E in metastatic colorectal cancer,” ecancermedicalscience, vol. 16, Art. no. 1489, 2022.
[39] J. Li et al., “Elastin is a key factor of tumor development in colorectal cancer,” BMC Cancer, vol. 20, Art. no. 217, 2020.
[40] G. Halsey et al., “Role of elastic fiber degradation in disease,” Biochim. Biophys. Acta Mol. Basis Dis., vol. 1869, Art. no. 166706, 2023.
[41] G. A. Cabral-Pacheco et al., “Matrix metalloproteinases and their inhibitors,” Int. J. Mol. Sci., vol. 21, Art. no. 9739, 2020.
[42] W. G. Stetler-Stevenson, “TIMP-2 in tissue homeostasis and cancer,” Am. J. Pathol., vol. 193, pp. 1336–1352, 2023.
[43] H.-L. Huang et al., “TIMP3 expression and prognosis in colorectal cancer,” Theranostics, vol. 9, pp. 6676–6689, 2019.
[44] V. E. Reyes, “Helicobacter pylori and its role in gastric cancer,” Microorganisms, vol. 11, Art. no. 1312, 2023.
[45] S. A. R. Shah et al., “Helicobacter pylori and gastric cancer,” RSC Adv., vol. 15, pp. 5558–5570, 2025.
[46] S. Salvatori et al., “Helicobacter pylori and gastric cancer: Pathogenetic mechanisms,” Int. J. Mol. Sci., vol. 24, Art. no. 2895, 2023.
[47] J. Baj et al., “Helicobacter pylori virulence factors,” Cells, vol. 10, Art. no. 27, 2020.
[48] E. Ierardi et al., “Coccoid forms of Helicobacter pylori,” Antibiotics, vol. 9, Art. no. 293, 2020.
[49] J. Ferlay et al., “Estimating global cancer incidence and mortality 2018,” Int. J. Cancer, vol. 144, pp. 1941–1953, 2019.
[50] C. Varon et al., “Helicobacters and cancer,” Semin. Cancer Biol., vol. 86, pp. 1138–1154, 2022.
[51] C. D. Iwu and C. J. Iwu-Jaja, “Gastric cancer epidemiology,” Hygiene, vol. 3, pp. 256–268, 2023.
[52] S. Ansari and Y. Yamaoka, “Survival of Helicobacter pylori in gastric acidity,” Helicobacter, vol. 22, Art. no. e12386, 2017.

[53] J. Machlowska et al., "Gastric cancer: Epidemiology and genomics," Int. J. Mol. Sci., vol. 21, Art. no. 4012, 2020.
[54] V. E. Reyes, "Helicobacter pylori immune response," Med. Res. Arch., vol. 10, Art. no. 3370, 2022.
[55] J. A. Ajani et al., "Gastric adenocarcinoma," Nat. Rev. Dis. Primers, vol. 3, Art. no. 17036, 2017.
[56] T. M. Jamal Eddin et al., "H. pylori and epithelial–mesenchymal transition," Heliyon, vol. 9, Art. no. e18945, 2023.
[57] A. Lanas and F. K. L. Chan, "Peptic ulcer disease," Lancet, vol. 390, pp. 613–624, 2017.
[58] D. Bravo et al., "Helicobacter pylori in human health and disease," World J. Gastroenterol., vol. 24, pp. 3071–3089, 2018.
[59] M. Pucułek et al., "Stem cells in digestive system surgery," Folia Morphol., vol. 80, pp. 13–19, 2021.
[60] R. J. Owen, "Helicobacter species classification," Br. Med. Bull., vol. 54, pp. 17–30, 1998.
[61] H. M. Wexler, "The genus Bacteroides," in The Prokaryotes, Berlin: Springer, 2014, pp. 459–484.
[62] S. L. W. On et al., "Minimal standards for describing new species," Int. J. Syst. Evol. Microbiol., vol. 67, pp. 5296–5311, 2017.
[63] Z. Y. Muñoz-Ramírez et al., "Whole genome sequence of H. pylori strains," Front. Cell. Infect. Microbiol., vol. 7, Art. no. 50, 2017.
[64] K. Thorell et al., "The Helicobacter pylori genome project," Nat. Commun., vol. 14, Art. no. 8184, 2023.
[65] J. K. Y. Hooi et al., "Global prevalence of Helicobacter pylori," Gastroenterology, vol. 153, pp. 420–429, 2017.
[66] A. Šterbenc et al., "Helicobacter pylori virulence genes," World J. Gastroenterol., vol. 25, pp. 4870–4884, 2019.
[67] Z. Sedarat and A. W. Taylor-Robinson, "H. pylori outer membrane proteins," Pathogens, vol. 13, Art. no. 392, 2024.
[68] A. Ali and K. I. AlHussaini, "Helicobacter pylori: Pathogenesis and treatment," Microorganisms, vol. 12, Art. no. 22, 2024.
[69] I. Sirit and R. M. Peek, "Immune evasion by Helicobacter pylori," Cell. Mol. Gastroenterol. Hepatol., vol. 19, Art. no. 101470, 2025.
[70] H. C. Sharndama and I. E. Mba, "Helicobacter pylori virulence mechanisms," Brazilian J. Microbiol., vol. 53, pp. 33–50, 2022.
[71] D. L. Weeks et al., "A H^+-gated urea channel," Science, vol. 287, pp. 482–485, 2000.
[72] C. Follmer, "Ureases as therapeutic targets," J. Clin. Pathol., vol. 63, pp. 424–430, 2010.
[73] M. Xiang et al., "Macrophage immunity in H. pylori infection," Front. Immunol., vol. 16, pp. 1–12, 2025.
[74] H. Shaalan et al., "Effect of urease inhibitors on H. pylori," Front. Microbiol., vol. 15, Art. no. 1464484, 2024.
[75] K. S. Johnson and K. M. Ottemann, "H. pylori chemotaxis," Curr. Opin. Microbiol., vol. 41, pp. 51–57, 2018.
[76] M. Halte et al., "Bacterial motility and flagellum length," bioRxiv, 2024, doi: 10.1101/2024.06.28.599820.
[77] H. Gu, "Role of flagella in H. pylori pathogenesis," Curr. Microbiol., vol. 74, pp. 863–869, 2017.
[78] J. Wizenty and M. Sigal, "H. pylori, microbiota and gastric cancer," Nat. Rev. Gastroenterol. Hepatol., vol. 22, pp. 296–313, 2025.
[79] S. Nejati et al., "Influence of CagA and VacA," Microb. Pathog., vol. 117, pp. 43–48, 2018.
[80] Y. Peng et al., "CagA-mediated ferroptosis in gastric cancer," Exp. Mol. Med., vol. 56, pp. 441–452, 2024.
[81] X. Chen et al., "Mutant p53 in cancer," Cell Death Dis., vol. 13, Art. no. 974, 2022.
[82] S. Ansari and Y. Yamaoka, "H. pylori virulence factors," Toxins, vol. 11, Art. no. 677, 2019.
[83] Z. Fazeli et al., "CagA-induced IL-8 secretion," Gastroenterol. Hepatol. Bed Bench, vol. 9, pp. S42–S46, 2016.
[84] J. M. Kim, "H. pylori toxins," in Helicobacter pylori, Singapore: Springer, 2023, pp. 89–102.
[85] N. J. Foegeding et al., "VacA toxin biology," Toxins, vol. 8, Art. no. 173, 2016.
[86] C. Unakal et al., "vacA genes and gastric disease," IJID Reg., vol. 14, Art. no. 100498, 2025.
[87] L. Jeyamani et al., "CagA and VacA genes," Indian J. Pathol. Microbiol., vol. 61, pp. 66–69, 2018.
[88] Y. S. Son et al., "VacA-induced mitochondrial damage," Biomaterials, vol. 314, Art. no. 122842, 2025.
[89] S. L. Benoit and R. J. Maier, "Helicobacter catalase and oxidative stress," J. Biol. Chem., vol. 291, pp. 23366–23373, 2016.
[90] A. Stent et al., "Superoxide dismutase in H. pylori infection," Helicobacter, vol. 23, Art. no. e12459, 2018.
[91] W. Durante et al., "Arginase and nitric oxide," Clin. Exp. Pharmacol. Physiol., vol. 34, pp. 906–911, 2007.
[92] J.-F. Liu et al., "Apoptosis in H. pylori infection," Microb. Pathog., vol. 150, Art. no. 104717, 2021.
[93] A. Mitrić and I. Castellano, "Targeting gamma-glutamyl transpeptidase," Free Radic. Biol. Med., vol. 208, pp. 672–683, 2023.
[94] L. Heinke, "Mitochondrial ROS and cell cycle," Nat. Rev. Mol. Cell Biol., vol. 23, p. 581, 2022.
[95] A. Corti et al., "Pathogenic effects of GGT," Free Radic. Biol. Med., vol. 160, pp. 807–819, 2020.
[96] S. You et al., "H. pylori outer membrane protein families," Microb. Pathog., vol. 206, Art. no. 107740, 2025.
[97] K. Vijay, "Toll-like receptors in immunity," Int. Immunopharmacol., vol. 59, pp. 391–412, 2018.

[98] X. Tang et al., “H. pylori lipopolysaccharide,” FEMS Microbiol. Rev., vol. 49, Art. no. fuaf034, 2025.
[99] M. J. Page et al., “LPS-induced cell signalling,” Chronic Stress, vol. 6, Art. no. 24705470221076390, 2022.
[100] S. S. Ghosh et al., “Intestinal barrier dysfunction,” J. Endocr. Soc., vol. 4, Art. no. bvz039, 2020.
[101] D. Doohan et al., “BabA–SabA roles in H. pylori adherence,” Toxins, vol. 13, Art. no. 485, 2021.
[102] K. I. Othman, S. Tofik, and J. Balaky, “Cellular and molecular biology research,” Cell Mol. Biol. Res., vol. 71, pp. 88–95, 2025.
[103] C. Xu et al., “Virulence of H. pylori outer membrane proteins,” Eur. J. Clin. Microbiol. Infect. Dis., vol. 39, pp. 1821–1830, 2020.
[104] D. A. Israel and R. M. Peek, “Mechanisms of H. pylori-induced gastric inflammation,” in Physiology of the Gastrointestinal Tract, 6th ed., Academic Press, 2018, pp. 1517–1545.
[105] M. Shirani et al., “Immunopathogenesis of H. pylori-induced gastric cancer,” Front. Microbiol., vol. 15, pp. 1–14, 2024.
[106] Q. Zhao et al., “Prevalence of babA, oipA, sabA genes,” Med. Microbiol. Immunol., vol. 209, pp. 565–577, 2020.
[107] Q. Zhao et al., “Outer inflammatory protein and IL-8,” Med. Microbiol. Immunol., vol. 209, pp. 621–630, 2020.
[108] M. L. Sallas et al., “oipA gene status and gastric cancer,” Arch. Microbiol., vol. 201, pp. 93–97, 2019.
[109] J. Liu et al., “Dendritic cell migration,” Cell. Mol. Immunol., vol. 18, pp. 2461–2471, 2021.
[110] L. L. de Lima Silva et al., “dupA gene and gastric disease,” Brazilian J. Microbiol., vol. 52, pp. 1921–1927, 2021.
[111] A. Talebi Bezmin Abadi and G. Perez-Perez, “Role of dupA in H. pylori virulence,” World J. Gastroenterol., vol. 22, pp. 10118–10123, 2016.
[112] A. Elbehiry et al., “H. pylori virulence genes and vaccines,” Front. Med., vol. 11, pp. 1–16, 2024.
[113] H.-W. Fu and Y.-C. Lai, “Neutrophil-activating protein of H. pylori,” Int. J. Mol. Sci., vol. 24, Art. no. 91, 2022.
[114] A. S. Tripathy et al., “Pro-inflammatory cytokines as biomarkers,” Arch. Virol., vol. 166, pp. 3301–3310, 2021.
[115] J. M. Storey and K. B. Storey, “Chaperone proteins,” Cell Stress Chaperones, vol. 28, pp. 455–466, 2023.
[116] O. M. Manna et al., “Heat shock proteins of H. pylori,” Int. J. Mol. Sci., vol. 26, Art. no. 5065, 2025.
[117] A. Karkhah et al., “H. pylori immune evasion strategies,” Microbiol. Res., vol. 218, pp. 49–57, 2019.
[118] X. Wang et al., “Immune microenvironment perturbation by H. pylori,” Biochim. Biophys. Acta Rev. Cancer, vol. 1879, Art. no. 189139, 2024.
[119] X. Wu et al., “Helper T cells in H. pylori infection,” Front. Immunol., vol. 16, pp. 1–12, 2025.
[120] Y. Zhang et al., “Innate immunity in H. pylori infection,” Helicobacter, vol. 30, Art. no. e70015, 2025.
[121] P. Malfertheiner et al., “Helicobacter pylori infection,” Nat. Rev. Dis. Primers, vol. 9, Art. no. 19, 2023.