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CORRELATION ON *H. PYLORI* INFESTATION TO THE DEVELOPMENT OF PREMALIGNANT LESION IN GASTRIC MUCOSA

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Abstract

Helicobacter pylori (*H. pylori*) is a microaerophilic, spiral-shaped Gram-negative bacterium that colonizes the gastric mucosa of nearly half the global population. Its presence is strongly linked to a multistep progression from chronic gastritis to gastric adenocarcinoma, mediated through premalignant mucosal changes such as atrophic gastritis, intestinal metaplasia, and dysplasia. Although this association is well established, emerging research in the past five years has uncovered novel molecular insights into host pathogen interactions, microbiome perturbations, and immune regulatory mechanisms that contribute to carcinogenesis. This study consolidates current knowledge on the pathophysiological mechanisms underlying *H. pylori*-induced mucosal transformation, emphasizes innovative diagnostic and prognostic tools, and explores promising preventive and therapeutic interventions aimed at intercepting the progression of premalignant gastric lesions.

Keywords

Helicobacter pylori, premalignant gastric lesions, Gastric carcinogenesis, chronic inflammation, Atrophic gastritis

INTRODUCTION

Gastric cancer remains a major global health challenge, ranking among the top five cancers in incidence and mortality worldwide (1) (2). Despite advances in diagnostic imaging, endoscopic surveillance, and surgical interventions, its prognosis is often poor due to late detection. This has fueled scientific interest in understanding the earliest steps of gastric carcinogenesis and the identification of high-risk patients before irreversible malignant transformation occurs (3). One of the most significant breakthroughs in this field was the discovery of *Helicobacter pylori* (*H. pylori*), a spiral-shaped, and Gram-negative, microaerophilic bacterium capable of persistently colonizing the harsh acidic environment of the stomach (4) (5). Epidemiological data indicate that over 50% of the world's population harbors *H. pylori*, yet only a fraction progress to premalignant lesions or cancer. This discrepancy highlights the multifactorial nature of disease progression, involving bacterial virulence, host genetic predisposition, environmental influences, and microbiome composition (6). The path from *H. pylori* infection to gastric cancer often follows the Correa cascade, which describes a histological sequence from chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and adenocarcinoma (7). The bacterium initiates this process through persistent inflammation, immune dysregulation, and direct epithelial damage. Its virulence factors, notably CagA and VacA, modulate host cell signaling, induce DNA damage, and alter apoptosis pathways,

creating a mucosal environment primed for malignant transformation (8) (9). In figure 1 provides a visual summary of the pathogenic mechanisms underpinning *H. pylori* associated gastric mucosal injury. Upon colonization, *H. pylori* uses urease to hydrolyze urea, producing ammonia and carbon dioxide, thereby creating a localized neutralized buffer zone that allows survival in gastric acidity (10). The bacterium adheres to the gastric epithelium, disrupting tight junction integrity and compromising the epithelial barrier. This damage triggers apoptosis via Fas receptor upregulation and pro-inflammatory cytokines such as IL-1β and TNF-α. Pathogenic mechanisms of *H. pylori* infection in gastric mucosa, showing urease-mediated neutralization of gastric acid, epithelial barrier disruption, immune cell recruitment, cytokine signaling, and apoptosis (11). The immune system mounts a vigorous yet ultimately ineffective response: macrophages release IL-12, promoting Th1 cell differentiation and IFN-γ secretion, while neutrophil recruitment is driven by IL-8 and other chemokines (12). However, *H. pylori* subverts these defenses by interfering with IL-2 mediated T cell activation and suppressing nitric oxide production, enabling long-term persistence. This chronic immune activation results in cytokine-induced changes in gastric physiology, which, over time, contribute to atrophic changes, intestinal metaplasia, and dysplasia (13).

Following colonization of the gastric mucosa, *H. pylori* initiates a cascade of pathological events that progressively remodel the epithelial landscape and predispose to malignant transformation (14). This process is classically described by the Correa cascade, in which normal mucosa first develops chronic active gastritis, followed by glandular atrophy, intestinal metaplasia, dysplasia, and ultimately adenocarcinoma (15) (16). Persistent infection is sustained by the bacterium's ability to evade immune clearance, aided by virulence factors such as cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), and outer inflammatory protein A (OipA) (17). CagA, translocated into gastric epithelial cells via a type IV secretion system, disrupts intracellular signaling through aberrant activation of SHP-2 phosphatase, causing cytoskeletal rearrangements, loss of cell polarity, and the initiation of epithelial mesenchymal transition (EMT) (18). VacA induces mitochondrial dysfunction, leading to apoptosis, and interferes with lysosomal degradation pathways to modulate autophagy in favor of bacterial survival (19). OipA amplifies inflammatory signaling by stimulating interleukin-8 (IL-8) secretion, thereby perpetuating neutrophil recruitment and oxidative damage. Collectively, these factors generate a microenvironment characterized by sustained oxidative stress, DNA damage, and abnormal epithelial turnover key prerequisites for the development of premalignant gastric lesions (20).

H. pylori-associated disease is the paradoxical immune response it elicits. While the host mounts a vigorous inflammatory reaction, this is insufficient for bacterial eradication, leading to chronic immune activation that is both damaging and self-perpetuating (21). Infected gastric epithelium produces IL-8 and other chemokines that recruit polymorphonuclear neutrophils (PMNs), while macrophages activated by bacterial components secrete IL-12, driving a T helper 1 (Th1)-polarized immune response with interferon-gamma (IFN-γ) production (22). This Th1-driven inflammation, while intended for pathogen clearance, contributes to epithelial injury and apoptosis through Fas receptor expression and pro-inflammatory cytokines such as IL-1β and tumor necrosis factor-alpha (TNF-α). *H. pylori*, however, has evolved to subvert these host defenses by suppressing IL-2-mediated T cell activation and inhibiting macrophage nitric oxide production, thereby ensuring its persistence within the gastric niche. Over time, these immune-mediated injuries cause cytokine-driven alterations in gastric physiology, including acid secretion changes and epithelial remodeling, which facilitate the histological progression toward atrophy, metaplasia, and dysplasia (23).

Recent research has significantly expanded the understanding of this process, revealing it to be more dynamic and multifactorial than previously believed. Large-scale genome-wide association studies have identified specific host genetic polymorphisms particularly in IL-1β, toll-like receptor 4 (TLR4), and mucin 1 (MUC1) that influence inflammatory intensity and mucosal resilience (24). For instance, IL-1β high-expression alleles amplify the inflammatory cascade and reduce gastric acidity, favoring bacterial persistence and progression to intestinal metaplasia. These genomic findings, when integrated with bacterial genotyping for virulence markers such as CagA and VacA, enable a precision-medicine approach to identifying high-risk individuals. In parallel, metagenomic sequencing has shown that the gastric microbiome undergoes persistent alterations even after successful *H. pylori* eradication (25). Notably, overrepresentation of nitrate-reducing bacteria such as *Neisseria* and *Lactobacillus* can sustain carcinogen formation through nitrosamine production, suggesting that microbiome composition itself may act as an independent promoter of premalignant changes (26).

The therapeutic landscape for *H. pylori*-induced premalignant lesions is evolving beyond traditional antibiotic eradication. While triple or quadruple therapy remains standard, antibiotic resistance is an increasing concern.

Innovative approaches such as CRISPR-Cas based bacteriophage therapy are being investigated to selectively target bacterial virulence genes without broadly disrupting the gastric microbiome (27). Probiotic and postbiotic interventions, including the use of *Lactobacillus reuteri* producing the antimicrobial metabolite reuterin, have demonstrated the ability to reduce bacterial adherence to epithelial cells and mitigate mucosal inflammation, potentially serving as adjunctive strategies (28). Another promising frontier is epigenetic therapy, aimed at reversing the "epigenetic memory" imprinted by *H. pylori* infection. Low-dose, localized delivery of DNA demethylating agents or histone deacetylase inhibitors could restore normal expression of silenced tumor suppressor genes, slowing or reversing lesion progression (29). Preventive immunization is also under active exploration, with nanoparticle-based peptide vaccines targeting CagA and VacA epitopes showing encouraging results in preclinical studies by eliciting both mucosal IgA and systemic IgG responses, which could be particularly impactful in high-prevalence regions with high reinfection rates (30).

Future research should concentrate on incorporating these strategies into clinical practice, emphasizing individualized therapy, early intervention, and mucosal homeostasis restoration in order to disrupt the progression from *H. pylori* colonization to gastric cancer.

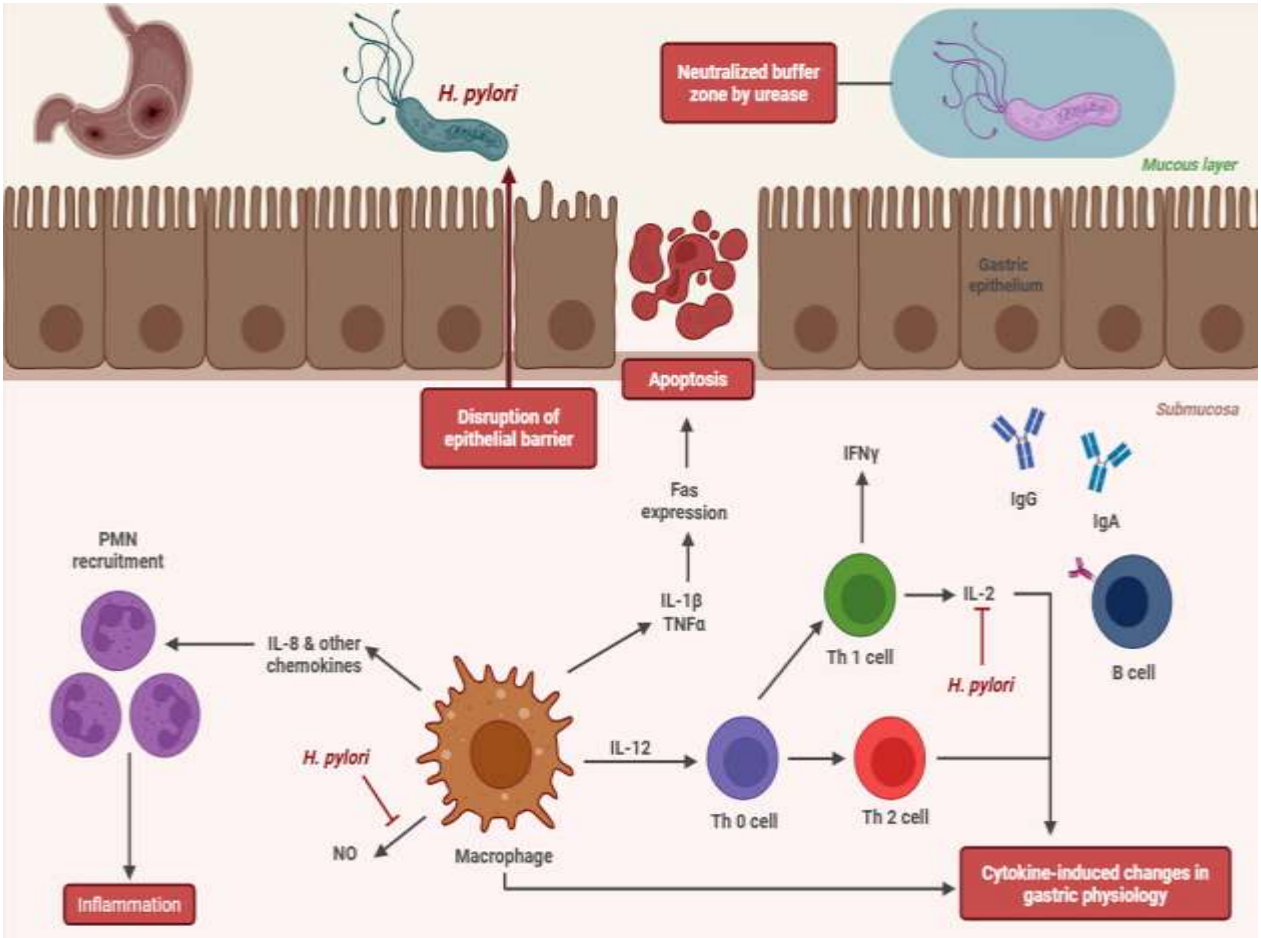

FIGURE.1 the figure illustrates the pathogenic mechanisms of *Helicobacter pylori* infection, showing its colonization of the gastric epithelium via urease-mediated neutralization and subsequent disruption of the epithelial barrier. Immune responses involve macrophage activation, cytokine release, Th cell differentiation, antibody production, and recruitment of polymorphonuclear (PMN) cells. These processes lead to apoptosis, chronic inflammation, and cytokine-induced alterations in gastric physiology, contributing to disease progression.

Heading	Aspect	Key Details	References
Epidemiology & Disease Burden	Global prevalence	*H. pylori* infects ~50% of population; gastric cancer ranks among top five cancers in incidence & mortality.	(1), (2)
	Risk progression	Only a fraction progress to premalignant lesions or cancer due to multifactorial influences.	(5)
Pathogenesis Overview	Correa cascade	Chronic gastritis, Atrophic gastritis, Intestinal metaplasia, Dysplasia, Adenocarcinoma.	(13)
	Gastric colonization	Urease-mediated ammonia production buffers acid; adhesion disrupts tight junctions.	(8)
Bacterial Virulence Factors	CagA	Disrupts SHP-2 signaling, induces EMT, cytoskeletal changes, cell polarity loss.	(15)
	VacA	Causes mitochondrial dysfunction, ER stress, apoptosis, alters autophagy.	(16)
	OipA	Triggers IL-8 secretion, perpetuates inflammation, and enhances neutrophil recruitment.	(17)
Immune Responses & Evasion	Th1-mediated inflammation	IL-8, IL-12, IFN-γ, TNF-α drive injury via Fas receptor apoptosis pathway.	(19)
	Immune evasion	Inhibits IL-2 activation of T cells, reduces macrophage NO production, and promotes persistence.	(18), (20)
Host Genetic Susceptibility	Inflammatory gene polymorphisms	IL-1β high-expression alleles reduce acidity & amplify inflammation; TLR4 & MUC1 variants linked to mucosal damage.	(21)
Microbiome Alterations	Dysbiosis in gastric mucosa	Persistent nitrate-reducing bacteria (*Neisseria*, *Lactobacillus*) generate carcinogenic nitrosamines.	(23)
Diagnostics & Risk Stratification	Genomic + bacterial profiling	Combines host SNPs with H. pylori virulence typing for high-risk patient identification.	(22)
	Metagenomic surveillance	Detects persistent carcinogenic microbiota post-eradication.	(23)
Innovative Therapeutic Strategies	CRISPR-Cas bacteriophage therapy	Gene-specific targeting of H. pylori virulence factors without disturbing commensals.	(24)
	Probiotic/postbiotic therapy	*Lactobacillus reuteri* producing reuterin inhibits adhesion & reduces inflammation.	(25)
	Epigenetic reprogramming	HDAC inhibitors & DNA demethylating agents restore tumor suppressor activity.	(26)
Vaccination Approaches	Nanoparticle-based peptide vaccines	Target CagA/VacA epitopes; elicit mucosal IgA & systemic IgG.	(27)
Prevention Strategies	High-prevalence region focus	Combined eradication + microbiome restoration to reduce recurrence risk.	(4)
Future Research Directions	Integrated multi-omics	Combining genomic, microbiome, and immunological profiling for precision prevention & therapy.	(3), (12)

TABLE 1 this table summarizes key epidemiological insights, pathogenic mechanisms, host- pathogen interactions, diagnostic approaches, and innovative therapeutic strategies in *Helicobacter pylori*-induced premalignant gastric lesions. References correspond to studies cited in the manuscript, highlighting both established and emerging research directions.

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