Advances in *Helicobacter pylori*-mediated oncogenic signaling pathways in gastric cancer: From pathological evolution to clinical application prospects (Review)

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Received January 7, 2026; Accepted April 27, 2026

DOI: 10.3892/ol.2026.15763

Abstract. *Helicobacter pylori* (*H. pylori*) infection constitutes a principal risk factor for gastric cancer (GC), however, the intricate oncogenic mechanisms underlying this association are not fully elucidated. The present review provides a comprehensive synthesis of the molecular pathways driving *H. pylori*-mediated gastric carcinogenesis, with a focus on core oncogenic signaling cascades including NF-κB, MAPK, Janus kinase/STAT and PI3K/AKT, as well as epigenetic regulatory mechanisms such as DNA methylation and non-coding RNAs. By integrating insights from single-cell sequencing and microbiome research, the crosstalk between *H. pylori* and the gastrointestinal microbiota is dissected, alongside their combined impact on the tumor microenvironment. Additionally, the present review summarizes key *H. pylori* virulence factors, most notably cytotoxin-associated gene A and vacuolating cytotoxin A, and delineates their functional contributions to tumor progression. The role of gastric stem cells in tumorigenesis and the reprogramming of their intrinsic signaling pathways are also elaborated. From a clinical standpoint, current progress in the identification of molecular diagnostic biomarkers, therapeutic targets and immunotherapeutic approaches is highlighted based on these mechanistic discoveries. Overall, the present review seeks to integrate basic research findings with clinical practice, providing valuable insights into promising directions for the early diagnosis and precision therapy of GC.

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Key words: Helicobacter pylori, gastric cancer, oncogenic signaling pathways, epigenetic regulation, gastrointestinal microbiota

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1. Introduction

Although the incidence and mortality of gastric cancer (GC) have declined worldwide over the past 5 decades, GC remains a substantial global health burden (1,2). In 2020, GC accounted for >1,000,000 new cases and ~768,000 deaths worldwide and with a particularly high disease burden in East Asia, *Helicobacter pylori* (*H. pylori*) infection remains a leading modifiable risk factor for GC (1,2). Approximately half of the world's population is colonized by *H. pylori*, yet its prevalence varies markedly across regions due to geographic, demographic and socioeconomic disparities (3). Despite this high global prevalence, only a small subset of infected individuals progress to gastric adenocarcinoma or mucosa-associated lymphoid tissue lymphoma. This observation suggests that gastric carcinogenesis is a multifactorial, stepwise process driven by intricate host-pathogen crosstalk, alongside additional environmental and genetic modifiers (3,4). This underscores the need to clarify the key molecular mechanisms linking *H. pylori* infection to gastric carcinogenesis.

The pathogenesis of *H. pylori*-associated GC follows a dynamic, progressive histopathological sequence known

as the Correa cascade which encompasses chronic active gastritis, atrophic gastritis, intestinal metaplasia, dysplasia and ultimately invasive carcinoma (5,6). This pathological progression is fueled by persistent bacterial colonization, which elicits chronic inflammation, oxidative stress and disruption of gastric epithelial homeostasis (7-10). *H. pylori* encodes a suite of virulence factors, including cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) which facilitate bacterial adherence, perturb host cell signaling pathways and induce DNA damage, collectively promoting genomic instability and oncogenic transformation (3,11,12). For example, CagA injection into gastric epithelial cells via a type IV secretion system (T4SS) drives aberrant activation of oncogenic cascades such as Ras-ERK, PI3K/AKT and Wnt/β-catenin (12). These signaling abnormalities contribute to epithelial-mesenchymal transition (EMT), enhanced cell proliferation and survival of transformed cells (11,13,14). Additionally, *H. pylori* infection induces epigenetic modifications including DNA methylation of tumor suppressor genes such as cadherin-1 (CDH1) and inhibitor of DNA binding 4 that further disrupt cellular regulatory networks and favor malignant progression (15,16). The main DNA damage patterns summarized in Table I include oxidative DNA damage, double-strand breaks, ribosomal restriction/digestion damage and microsatellite instability (17-27).

Notably, GC development is not solely attributed to direct bacterial effects but also involves complex interactions with the host immune system and gastric microenvironment. *H. pylori* infection triggers innate and adaptive immune responses via pathogen-associated molecular patterns that engage pattern recognition receptors on gastric epithelial cells and immune cells, thereby activating NF-κB, MAPK and Janus kinase (JAK)/STAT signaling and inducing the production of pro-inflammatory cytokines and chemokines, such as IL-1β, IL-6, IL-8, TNF-α and C-C motif chemokine ligand 2 (1,28). These mediators subsequently promote the recruitment of neutrophils, macrophages, dendritic cells and multiple T cell subsets, including $CD4^+$ T cells, $CD8^+$ T cells and regulatory T cells, into the gastric mucosa. Persistent immune cell infiltration further sustains chronic inflammation and gradually contributes to the establishment of an immunosuppressive tumor microenvironment (TME). However, the bacterium develops elaborate immune evasion mechanisms, which support long-term colonization and sustain chronic inflammation, paradoxically creating a tumor-permissive milieu. These strategies include modulation of immune checkpoint pathways [such as programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1)], induction of regulatory T cells and skewing of macrophage polarization, all of which dampen effective antitumor immunity (28-30). For instance, *H. pylori*-mediated upregulation of PD-L1 through signaling pathways involving AlkB homolog 5 RNA demethylase and heat shock protein family A member 4 impairs $CD8^+$ T cell cytotoxicity, enabling immune escape of GC cells (31,32). Furthermore, the *H. pylori*-altered TME is characterized by metabolic reprogramming including enhanced glycolysis and lactate accumulation, that suppresses immune cell function and promotes tumor progression (33,34). Although *H. pylori* is widely recognized as the principal pathogenic bacterium driving gastric carcinogenesis, accumulating evidence suggests that other members of the gastric microbiota may also participate in this process (35-37). These non-*Helicobacter* microorganisms may contribute to tumor initiation and progression by promoting microbial dysbiosis, producing pro-inflammatory or genotoxic metabolites and reshaping the local immune microenvironment (38-40). Therefore, gastric carcinogenesis should be viewed not only as a consequence of *H. pylori* infection, but also as a multifactorial process influenced by broader microbial interactions within the gastric niche.

Previous advances in molecular biology and multi-omics technologies have expanded understanding of the gastric microbiome beyond *H. pylori*, revealing that perturbations in microbial community composition and function may modulate gastric carcinogenesis (41,42). Dysbiosis involving non-*Helicobacter* species (such as *Streptococcus*, *Fusobacterium nucleatum* and *Veillonella*) has been linked to precancerous lesions and GC, potentially through mechanisms including chronic inflammation, production of genotoxic metabolites and immune modulation (43,44). These findings suggest that microbial interactions within the gastric niche, in conjunction with *H. pylori* infection, contribute to the multifaceted pathogenesis of GC.

Clinically, *H. pylori* eradication remains a cornerstone of GC prevention, with evidence supporting its role in reducing gastric adenocarcinoma incidence and improving outcomes in patients with early-stage GC (45). Nevertheless, eradication therapy fails to completely eliminate cancer risk particularly in patients with pre-existing atrophic gastritis or intestinal metaplasia. This underscores the need for improved risk stratification and novel therapeutic strategies targeting the molecular and immunological sequelae of infection (5,16). Integrating insights from recent research on *H. pylori*-mediated signaling pathways, immune evasion and microbiome alterations holds promise for developing precision medicine approaches to optimize GC prevention and treatment.

Due to the complexity of *H. pylori*-associated gastric carcinogenesis, a focused review of the core oncogenic signaling pathways is required. Therefore, the present review concentrates on the major virulence factors, key signaling cascades and selected translational implications most directly relevant to *H. pylori*-mediated tumorigenesis, with the aim of providing a clearer mechanistic framework for future research and clinical application.

2. Tumorigenic factors of *H. pylori* and their molecular mechanisms

H. pylori promotes gastric carcinogenesis primarily through a set of virulence factors that disrupt host cellular signaling, induce chronic inflammation and alter genomic and epigenetic stability. Among these, CagA and VacA are the most extensively characterized and function as central regulators of multiple oncogenic pathways. The present section focuses on the key virulence factors and their molecular mechanisms, with particular emphasis on their roles in modulating epithelial integrity, immune responses and signaling networks.

CagA and VacA virulence factors: Structure and function. Among the virulence factors of *H. pylori*, CagA and VacA are the most extensively studied due to their critical roles

Table I. *H. pylori*-induced DNA damage types.

Type of DNA damage	Mechanism and effect	(Refs.)
Oxidative DNA damage	*H. pylori*-induced oxidative stress leads to formation of 8-hydroxy-2'-deoxyguanosine and other oxidized DNA base adducts, contributing to the mutations and genomic instability.	(17-19)
Double-strand breaks	*H. pylori* secretes virulence factors causing various double-strand breaks. Improper repair of these breaks may result in chromosomal rearrangements.	(12,20-22)
Ribosomal restriction and digestion damage	*H. pylori* activates ribosomal enzymes that can cleave RNA, adding to genomic instability.	(23)
Microsatellite instability	Virulent strains of *H. pylori* are linked to high-frequency microsatellite instability, increasing mutation rates in microsatellite sequences.	(24-27)

H. pylori, Helicobacter pylori.

in pathogenesis and carcinogenesis (46). The CagA protein is delivered into gastric epithelial cells via a T4SS, where it disrupts normal cellular signaling pathways (47). Upon injection, CagA undergoes tyrosine phosphorylation at EPIYA motifs, leading to aberrant activation of multiple signaling cascades that promote genetic instability, dysregulation of cell proliferation and EMT, processes which are fundamental to tumorigenesis (48,49). The structural complexity of CagA includes variable EPIYA motif patterns, which modulate its oncogenic potential and interaction with host proteins, contributing to geographic differences in disease outcomes (50). Mechanistically, this geographic variation is largely attributed to differences in the C-terminal EPIYA architecture of CagA. Western-type CagA typically contains EPIYA-A, EPIYA-B and one or more EPIYA-C segments, whereas East Asian-type CagA commonly contains an EPIYA-D segment instead of EPIYA-C (46). The EPIYA-D motif exhibits stronger binding affinity for SHP-2 than the EPIYA-C motif, resulting in more potent activation of downstream oncogenic signaling, cytoskeletal rearrangement, loss of epithelial polarity and the 'hummingbird' phenotype (46). Therefore, the predominance of East Asian-type CagA strains may partly explain the higher incidence and more severe clinical outcomes of *H. pylori*-associated gastric diseases in East Asian populations. However, these geographic differences should be interpreted as the result of interactions between bacterial virulence genotypes, host genetic susceptibility, dietary habits and environmental factors, rather than CagA polymorphism alone.

VacA, a secreted multifunctional toxin present in nearly all *H. pylori* strains, exerts its pathogenic effects through multiple mechanisms (51). It traverses several membrane barriers to enter host cells, where it forms anion-selective channels in endosomal membranes, leading to vacuole formation, disruption of mitochondrial functions and induction of apoptosis (52,53). VacA also modulates immune responses by interfering with antigen presentation and T cell activation, thereby promoting chronic inflammation and immune evasion (54). The structure of the toxin includes signal (s), intermediate and middle (m) regions, with different allelic variants (such as s1/m1, s1/m2 and s2/m2) associating with variation in cytotoxic activity and clinical outcomes (55,56). Notably, VacA disrupts mitochondrial membrane potential and perturbs endocytic trafficking, which contributes to the imbalance between cell survival and apoptosis, fostering a microenvironment conducive to carcinogenesis (52). Together, CagA and VacA act synergistically to disrupt gastric epithelial integrity and promote a tumor-permissive microenvironment characterized by persistent inflammation and impaired immune clearance (57,58). In addition to these two major virulence factors, other bacterial components such as urease, flagella and adhesins (blood group antigen-binding adhesion and sialic acid-binding adherence) mainly contribute to colonization and sustained host interaction (59,60). Table II summarizes the core mechanisms and functional contributions of major *H. pylori* virulence factors involved in gastric carcinogenesis. The signaling pathways summarized in Table II include STAT3, NF-κB, Wnt/β-catenin, MAPK, PI3K/AKT, Hippo and related cascades (61-67).

At the bacterial intracellular level, VacA transport is mediated by an intrabacterial nanotransportation system involving the MreB cytoskeletal filament, which facilitates its localization and secretion, underlining the complexity of its delivery mechanism (68). The regulation of these virulence factors is also influenced by bacterial small RNAs and environmental factors such as nickel concentration, which modulate expression and contribute to bacterial adaptation and persistence (69). Importantly, circulating levels of CagA and VacA proteins have been detected in some patients infected with *H. pylori*, suggesting systemic exposure that may have implications beyond the gastric mucosa (70). Examples of these extra-gastric implications include vascular injury and systemic immune modulation. CagA-containing extracellular vesicles have been reported to circulate in the serum and may deliver functional CagA to distant tissues, providing a potential mechanism by which *H. pylori* infection influences non-gastric organs (47,48). Experimental evidence suggests that CagA-positive *H. pylori* infection can promote endothelial oxidative stress, impair endothelial function and accelerate early atherosclerotic changes through exosome-mediated ROS formation (49). In addition, VacA is recognized as an immunomodulatory toxin that can interfere with T-cell activation and antigen-presenting cell function, thereby contributing to immune tolerance and persistent infection (54,57). Therefore, systemic exposure to CagA and VacA may be relevant not

Table II. Signaling pathways activated by *H. Pylori*.

Signaling pathways	Molecular mechanisms involved in gastric cancer induced by *H. pylori*	(Refs.)
STAT3	*H. pylori* activates the STAT3 pathway through upregulation of IL-6, CagA-mediated SHP-2 activation and TLR2 interaction. STAT3 regulates downstream target genes involved in cellular processes such as development, proliferation, differentiation, EMT, invasion, and metastasis.	(61-63)
NF-κB	*H. pylori* activates NF-κB through direct activation by CagA, IKK kinase, and upregulation of pro-inflammatory factors. NF-κB transcriptionally regulates genes involved in cell cycle progression, apoptosis inhibition, and cross-regulates with other tumor signaling pathways.	(26,61,64)
Wnt/β-catenin	*H. pylori* activates the Wnt/β-catenin pathway through CagA-mediated accumulation and nuclear translocation of β-catenin. Activation of this pathway disrupts cell cycle regulation, inhibits apoptosis, induces EMT and promotes tumor cell proliferation, motility, and invasion. Cross-regulation between Wnt/β-catenin and other pathways enhances oncogenic effects.	(61,65,66)
Other	*H. pylori* activates additional signaling pathways including the MAPK pathway (ERK, JNK and p38), PI3K/AKT pathway, Hippo pathway, and various other pathways (HGF/Met, TGF-β, Hedgehog and Notch). These pathways are involved in regulating proliferation, survival, migration, invasion, differentiation, apoptosis, stem cell properties, microRNA map, and exhibit complex cross-regulatory interactions with each other and with the classical pathways.	(61,65,67)

CagA, cytotoxin-associated gene A; EMT, epithelial-mesenchymal transition; TLR2, toll like receptor 2; HGF/Met, hepatocyte growth factor/mesenchymal-epithelial transition.

only to gastric carcinogenesis but also to extra-gastric manifestations such as vascular inflammation, atherosclerosis, and broader immune dysregulation.

In summary, CagA and VacA are structurally and functionally distinct but synergistically act to disrupt gastric epithelial integrity, modulate immune responses and promote oncogenic signaling. Their interplay is central to *H. pylori*-induced gastric carcinogenesis, making them critical targets for therapeutic intervention and vaccine development (53,71). Understanding the molecular mechanisms of these virulence factors provides insight into the pathophysiology of *H. pylori* infection and guides clinical strategies aimed at preventing and managing GC.

DNA methylation and epigenetic regulation. H. pylori infection is a well-established risk factor for GC, and accumulating evidence has elucidated its role in inducing aberrant DNA methylation and epigenetic dysregulation of tumor suppressor genes, which contributes to gastric carcinogenesis. *H. pylori* infection promotes abnormal hypermethylation of CpG islands in promoter regions of multiple tumor suppressor genes, leading to their transcriptional silencing and subsequent dysregulation of gene expression critical for cell cycle control, DNA repair and apoptosis (72). For instance, genes such as CDH1, Twist family basic helix-loop-helix transcription factor 1, Dickkopf-3, secreted frizzled-related protein 1 and empty spiracles homeobox 1 exhibit increased methylation in *H. pylori*-infected gastric mucosa, associating with precancerous lesions and GC development (73,74). This hypermethylation is often persistent following *H. pylori* eradication, reflecting a residual risk for metachronous GC (75,76). Mechanistically, *H. pylori* virulence factors, including CagA, induce DNA methyltransferase (DNMT) expression, such as DNMT1 and DNMT3B, which catalyze methylation of specific gene promoters such as Krüppel-like factor 4 and inhibitor of DNA binding 4, resulting in their downregulation and facilitating tumor progression (15,77). Moreover, the methylation status of these genes is associated with molecular subtypes of GC, including the CpG island methylator phenotype, and is associated with clinicopathological features such as tumor differentiation and stage (74). Beyond DNA methylation, epigenetic regulation also involves non-coding RNAs (ncRNAs): MicroRNAs (miRNAs) and long ncRNA (lncRNAs) are key post-transcriptional regulators modulated by *H. pylori* infection. Aberrant methylation of miRNA promoters, such as miR-124, leads to their silencing, which in turn affects oncogenic pathways and gene expression networks implicated in gastric carcinogenesis (78). lncRNAs such as CRYM-AS1 and LINC00511 are epigenetically regulated and contribute to GC progression by recruiting epigenetic modifiers such as enhancer of zeste homolog 2 to target promoters, leading to transcriptional repression of tumor suppressors and activation of oncogenic pathways including PI3K/AKT (79,80). Furthermore, the interplay between DNA methylation and lncRNAs shapes the TME and influences immune responses, potentially affecting immunotherapy efficacy (81). At the bacterial level, *H. pylori* itself exhibits diverse DNA methylation patterns that may regulate bacterial gene expression and virulence, indirectly influencing host epigenetic landscapes (82,83). The cumulative evidence

underscores that *H. pylori*-induced DNA methylation and epigenetic modifications constitute a complex regulatory network that disrupts normal gene expression, promotes malignant transformation and sustains gastric tumorigenesis. These epigenetic alterations hold promise as biomarkers for early detection, risk stratification and therapeutic targets in GC, with ongoing research aiming to translate these insights into clinical applications (6,84,85).

Major oncogenic signaling pathway activation. H. pylori infection acts as a pivotal driver in gastric carcinogenesis, primarily by triggering multiple oncogenic signaling pathways. These pathways synergistically regulate inflammation, cell proliferation, cell survival and TME remodeling. Among these cascades, the NF-κB pathway occupies a central role, as it mediates inflammatory responses and elicits cell survival signals that are crucial for TME formation (86). *H. pylori* infection can activate both classical and alternative NF-κB pathways in gastric epithelial cells, with the bacterial virulence factor CagA and other bacterial components serving as key triggers for this activation (86). The classical NF-κB pathway is initiated through TRAF-interacting protein with forkhead-associated (FHA) domain (TIFA)/TNF receptor associated factor (TRAF) 6 interactions, which in turn activate transforming growth factor β-activated kinase 1. By contrast, the alternative pathway involves TIFA/TRAF2 interactions that induce cellular inhibitor of apoptosis protein-1 degradation, thereby sustaining NF-κB signaling. This dual activation pattern leads to the upregulation of pro-inflammatory cytokines, including IL-6, IL-10 and VEGF. These cytokines not only perpetuate chronic inflammation but also hinder dendritic cell maturation and facilitate immune escape, ultimately fostering a pro-tumorigenic microenvironment (28,87-89). Moreover, NF-κB activation induces the expression of oncogenic microRNAs such as miR-18a-3p and miR-4286. These miRNAs have been reported to suppress the tumor suppressor gene benzodiazepine receptor (peripheral) associated protein 1, thereby promoting proliferation, migration and malignant progression in *H. pylori*-associated GC (90).

Concurrently, the MAPK and JAK/STAT signaling cascades serve critical roles in regulating cell proliferation, differentiation and immune evasion during *H. pylori* infection. *H. pylori* can activate the MAPK pathway, including the ERK and p38 kinase subfamilies. This activation contributes to increased expression of MMPs (such as MMP-10), which degrade extracellular matrix (ECM) components and promote tumor invasion and metastasis. The JAK/STAT pathway, particularly the STAT1 and STAT3 isoforms, is activated in response to *H. pylori*-induced cytokines, initiating transcriptional programs that support immune escape and tumor growth. Specifically, STAT3 activation, driven by downregulation of miR-375, enhances the secretion of IL-6, IL-10 and VEGF. This further promotes the differentiation of immature dendritic cells and suppresses effective antitumor immune responses. Additionally, *H. pylori* fibroblast growth factor 4 expression via STAT3, establishes a feedforward loop involving SRC kinase. This loop protects gastric epithelial cells from DNA damage and apoptosis, thereby facilitating tumorigenesis (28,88,91,92). Aurora kinase A (AURKA), another oncogenic mediator upregulated in *H. pylori* infection, modulates STAT3 and c-Myc to enhance cell proliferation and genomic instability (93). Furthermore, RAS protein activator like-2, whose expression is induced by NF-κB, activates the AKT/β-catenin axis, promoting tumor spheroid formation and chemoresistance (94).

The PI3K/AKT pathway serves as a central regulator of cell metabolism, proliferation and anti-apoptotic signaling in *H. pylori*-associated GC. *H. pylori*-induced activation of the PI3K/AKT/mTOR signaling cascade leads to NF-κB activation and upregulation of MMPs, thereby enhancing the invasive and migratory capabilities of gastric epithelial cells. Notably, antioxidants such as astaxanthin can suppress this pathway, reducing tumor invasiveness. The PI3K/AKT axis also contributes to the acquisition of cancer stem cell (CSC)-like properties through CagA-dependent mechanisms. This process involves downstream effectors such as FOXO3a, which is inhibited by AKT-mediated phosphorylation and subsequent cytoplasmic translocation, events that promote stemness and tumor progression. Additionally, the hypoxia-inducible factor-1 α (HIF-1α)-mediated hypoxic response is upregulated in *H. pylori* infection, particularly in the presence of the East Asian-type CagA variant. This upregulation intensifies reactive oxygen species production and enhances tumor cell migration and invasion. HIF-1α further induces the expression of oncogenic factors such as vasorin (VASN), which activates the collagen type IV α 1 (COL4A1)/PI3K/AKT pathway to amplify tumor growth (91,95-97).

Finally, the Hippo pathway, via its effectors yes-associated protein (YAP) and TAZ, is dysregulated in GC and modulated by *H. pylori* infection. *H. pylori* can alter the levels of integrin-linked kinase, leading to suppression of Hippo signaling and activation of YAP (98). Activated YAP drives tumor progression and the release of inflammatory cytokines (98). Disabled-2, whose expression is upregulated by STAT3 in response to *H. pylori*, acts as a scaffold protein that facilitates SRC-mediated phosphorylation events, thereby enhancing YAP transcriptional activity (99). Similarly, aberrant expression of G protein subunit β-4, induced by *H. pylori* through NF-κB and Tet methylcytosine dioxygenase 1-mediated promoter demethylation, promotes oncogenic behaviors via the Hippo-YAP1 signaling pathway (100). The mechanosensor PIEZO1 is also upregulated downstream of NF-κB, which in turn activates YAP1. This activation leads to the secretion of connective tissue growth factor, a cytokine that recruits cancer-associated fibroblasts and remodels the TME to support cancer progression. Targeting the Hippo-YAP axis and its upstream regulators thus represents a promising therapeutic strategy (98,100-103).

Collectively, these signaling pathways (NF-κB, MAPK, JAK/STAT, PI3K/AKT and Hippo) are intricately activated by *H. pylori* infection, forming a complex regulatory network that drives gastric carcinogenesis. This network promotes inflammation, cell proliferation, immune evasion, metabolic adaptation and TME remodeling. Understanding the mechanisms underlying these pathways provides critical insights into the molecular pathogenesis of *H. pylori*-induced GC and highlights potential therapeutic targets for clinical intervention (Fig. 1).

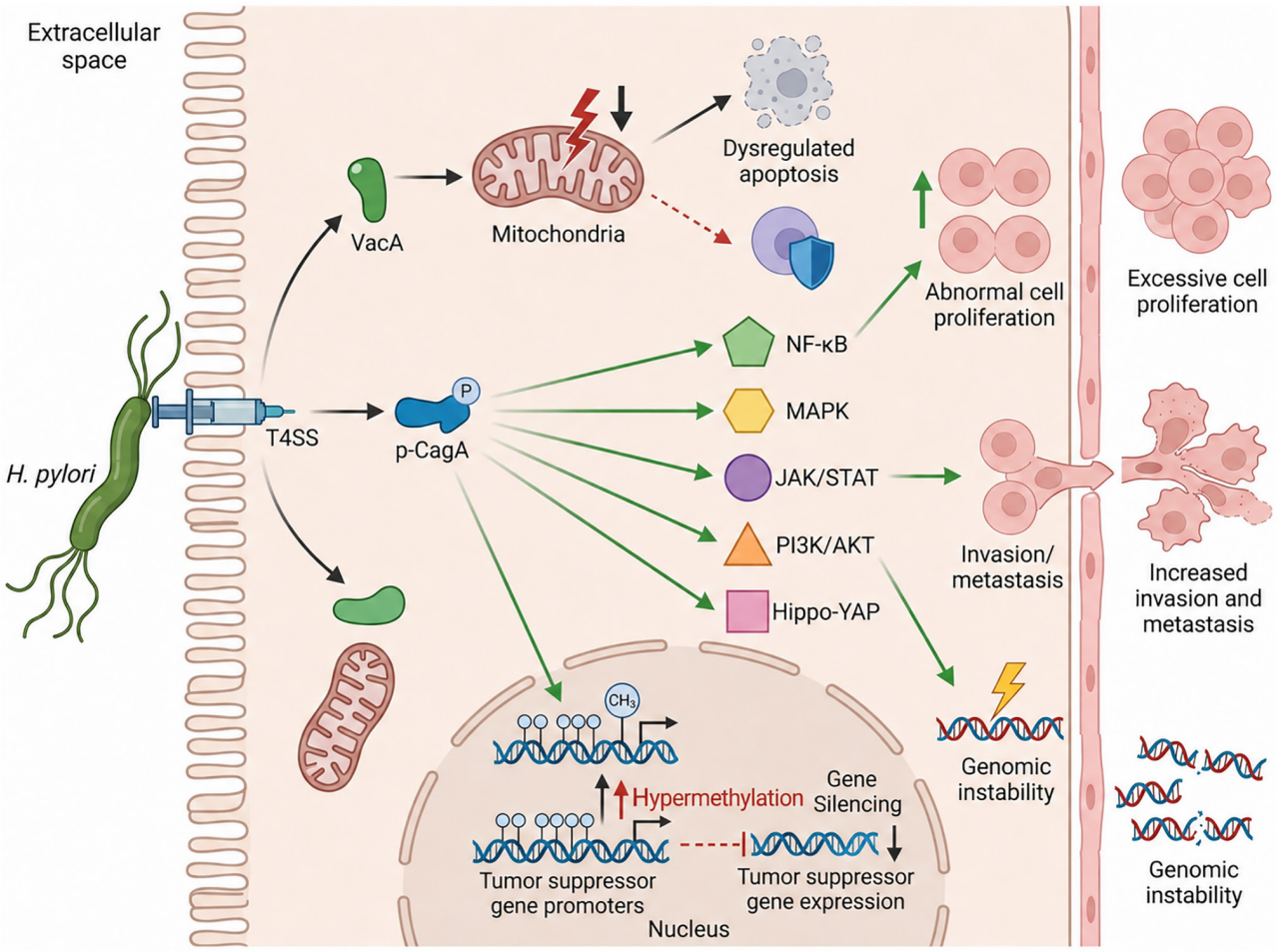

Figure 1. Mechanistic model of *H. pylori*-mediated oncogenic signaling in gastric epithelial cells. *H. pylori* delivers p-CagA via the T4SS and secretes VacA, which localizes to mitochondria. p-CagA propagates downstream signaling through activation of NF-κB, MAPK, JAK/STAT, PI3K/AKT and Hippo-YAP pathways. These cascades induce dysregulated apoptosis, excessive cell proliferation, and increased invasion/metastasis. Persistent stimulation leads to genomic instability. Meanwhile, *H. pylori* induces hypermethylation of tumor suppressor gene promoters, resulting in their transcriptional silencing and loss of function. This integrated network of signaling cascades and epigenetic modifications drives gastric carcinogenesis. *H. pylori*, *Helicobacter pylori*; Vac A, vacuolating cytotoxin A; p-CagA, phosphorylated cytotoxin-associated gene A; YAP, yes-associated protein; T4SS, type IV secretion system; JAK, Janus kinase.

3. Interaction between the gastrointestinal microbiota and *H. pylori* and their tumorigenic effects

H. pylori is the primary microbial driver of gastric carcinogenesis, but increasing evidence suggests that infection-associated changes in the gastric microbiota may further influence disease progression. Rather than acting as independent initiators of tumorigenesis, non-*Helicobacter* microbial communities are more plausibly considered secondary modifiers that amplify chronic inflammation, alter local metabolic conditions and reshape the TME. The following section therefore focuses on how *H. pylori*-associated microbial dysbiosis and microenvironmental remodeling may reinforce gastric carcinogenesis.

Gastric microbiota dysbiosis and tumor-promoting metabolites. H. pylori infection perturbs the fine-tuned equilibrium of the gastric microbiota, culminating in dysbiosis that is typified by diminished microbial diversity and altered community composition (Fig. 2) (104). During the early phase of gastritis, the dominance of *H. pylori* suppresses the colonization of other bacterial taxa, thereby fostering a gastric microenvironment with reduced microbial heterogeneity (104). Notably, as gastric lesions advance toward malignancy, the abundance of *H. pylori* declines progressively, and this niche is occupied by oral and intestinal-derived pathogenic bacteria including *Fusobacterium nucleatum*, *Streptococcus* and *Lactobacillus*, all of which exert pro-carcinogenic effects via multiple mechanisms (42,105-107). Mechanistically, *F. nucleatum* can adhere to and invade epithelial or tumor cells through virulence factors such as FadA, thereby disrupting E-cadherin-mediated cell adhesion and activating Wnt/β-catenin signaling, which promotes epithelial proliferation, EMT, invasion and metastatic potential (104). In addition, *F. nucleatum*-derived microbial components can activate TLR/NF-κB-dependent inflammatory signaling and induce cytokines such as IL-1β, IL-6, IL-8 and TNF-α, while Fap2-mediated interaction with TIGIT on T cells and natural killer cells may attenuate anti-tumor immune cytotoxicity (104). *Streptococcus* species may contribute to carcinogenesis by participating in nitrate/nitrite reduction and the formation of N-nitroso compounds or acetaldehyde, thereby increasing genotoxic stress and sustaining chronic

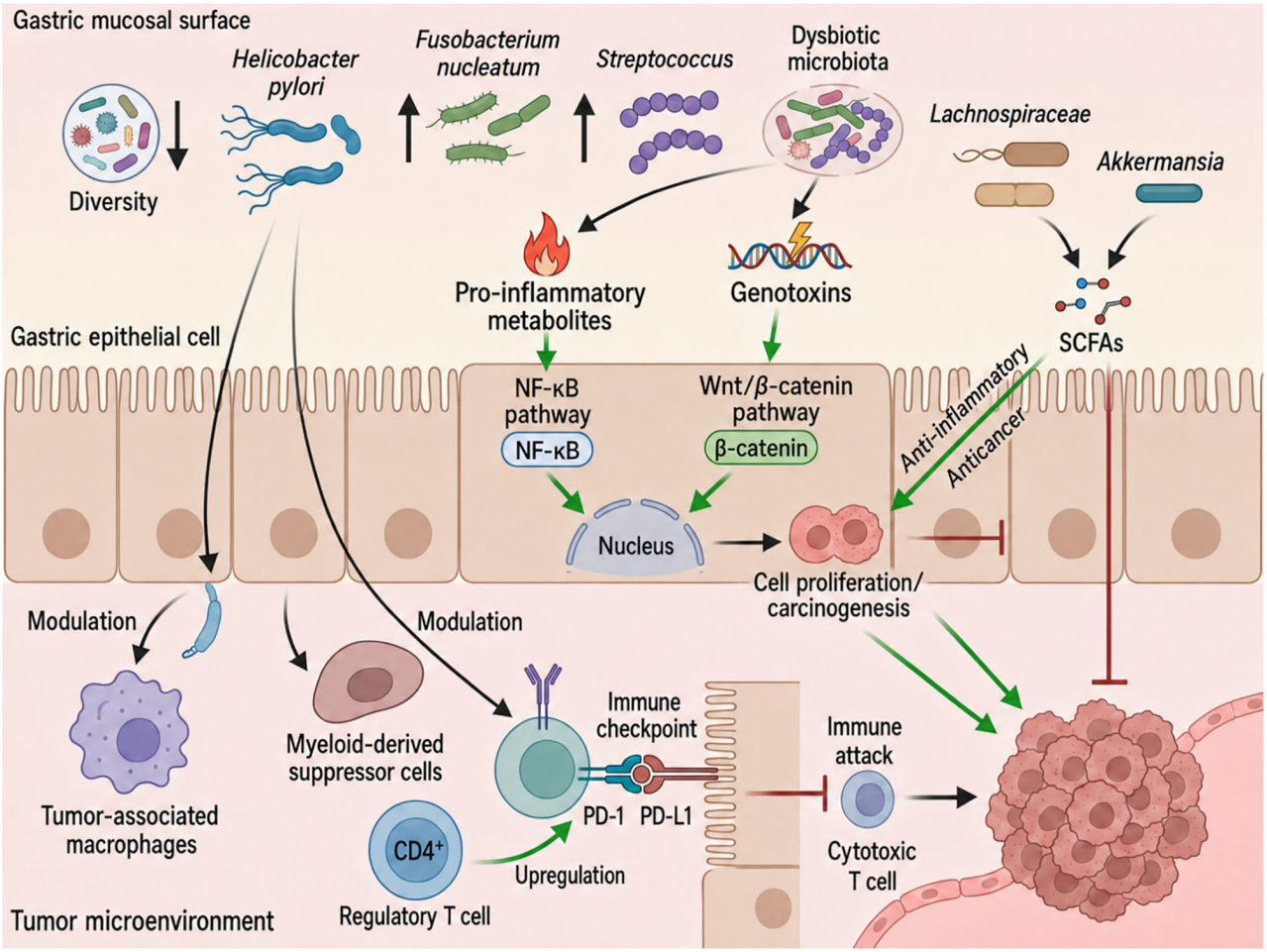

Figure 2. Gastric microbiota regulate gastric carcinogenesis and antitumor immunity. *Helicobacter pylori* infection induces dysbiosis, enriching pro-tumorigenic bacteria such as *Fusobacterium nucleatum* and *Streptococcus*. These pathogens activate NF-κB and Wnt/β-catenin oncogenic pathways, promote DNA damage and remodel the tumor microenvironment to suppress cytotoxic T cell responses via immune checkpoint upregulation. Beneficial commensals (such as *Lachnospiraceae* and *Akkermansia*) produce SCFAs to exert anti-inflammatory and anticancer effects. PD-1 programmed cell death-1; PD-L1, programmed death-ligand 1; SCFAs, short-chain fatty acids.

mucosal inflammation (43,44,106). Overgrowth of lactic acid-producing bacteria, including certain *Lactobacillus* species, may further reshape the metabolic niche through lactate accumulation, ROS production, and acidification of the tumor microenvironment, which can support tumor cell survival, angiogenesis, EMT and immune suppression (105-107). Therefore, these non-*H. pylori* taxa are more appropriately regarded as secondary microbial modifiers that amplify *H. pylori*-primed epithelial injury, inflammatory signaling, metabolic reprogramming, and tumor microenvironment remodeling rather than acting as independent initiators of gastric carcinogenesis (104-107).

These microbial alterations are accompanied by changes in the metabolic profile of the gastric niche. Dysbiotic communities may generate pro-inflammatory and potentially genotoxic metabolites that contribute to epithelial injury, DNA damage and sustained inflammatory signaling (108-110). In parallel, *H. pylori*-associated dysbiosis may impair local immune surveillance by altering the composition and function of immune cell populations within the gastric microenvironment (111,112). This immune imbalance further sustains chronic inflammation and weakens effective antitumor responses (110,113). In this way, microbial dysbiosis interacts with epithelial injury, inflammatory signaling, and host regulatory changes to exacerbate gastric carcinogenesis (39,106).

Overall, *H. pylori*-associated gastric microbiota dysbiosis contributes to a tumor-permissive microenvironment characterized by persistent inflammation, metabolic imbalance and impaired immune surveillance. Although these microbial changes are unlikely to represent independent initiating events, they may substantially amplify the carcinogenic effects of chronic *H. pylori* infection.

Protective bacteria and their anti-inflammatory effects. Specific commensal bacteria residing in the gut generate metabolites, with short-chain fatty acids (SCFAs), particularly butyrate, being prominent examples. These metabolites exhibit robust anti-inflammatory and anti-carcinogenic activities, which may mitigate the tumor-promoting effects triggered by *H. pylori* infection. SCFAs, encompassing butyrate, propionate and acetate, are end products of dietary fiber fermentation mediated by beneficial gut microbial taxa, such as members of the Lachnospiraceae family and *Faecalibaculum* species (106,114,115).

Mechanistically, protective commensals may attenuate inflammatory responses, support mucosal barrier function and

modulate cytokine production, thereby reducing the persistence of a tumor-promoting inflammatory milieu (106,116,117). Nevertheless, current evidence does not support the view that such bacteria can fully offset the dominant carcinogenic influence of chronic *H. pylori* infection (23,118,119). A reduction in beneficial commensals, together with overgrowth of pro-inflammatory taxa, may favor oxidative stress and persistent inflammation, both of which support gastric carcinogenesis. Thus, the balance between potentially protective and tumor-promoting microbial communities may influence the severity of *H. pylori*-associated mucosal injury, even though *H. pylori* itself remains the central carcinogenic determinant. In addition, natural compounds such as pectic oligosaccharides promote the proliferation of beneficial bacteria and enhance mucosal immunity. These effects lead to increased secretion of immunoglobulin A and reduced production of pro-inflammatory cytokines, which collectively contribute to the maintenance of gut homeostasis and protection against inflammation-driven carcinogenesis (120).

To summarize, protective gut commensal bacteria and their anti-inflammatory metabolites play a pivotal role in counteracting *H. pylori*-induced gastric carcinogenesis. Their mechanisms of action include regulating immune responses, preserving epithelial barrier function and maintaining microbial equilibrium. These findings highlight potential avenues for the development of preventive and therapeutic interventions for GC.

4. Gastric stem cells, tumor-initiating cells and signaling pathways in tumor progression

GC initiation and progression are driven by intricate interactions between gastric stem cells (GSCs), tumor-initiating cells (TICs) and dysregulated signaling pathways, particularly under pathological stimuli such as *H. pylori* infection and chronic inflammation. Accumulating evidence indicates that GSC heterogeneity and their malignant transformation into TICs serve as critical initiating events in GC carcinogenesis, while reprogramming of stem cell-related signaling cascades and aberrant activation of oncogenes further propel tumor progression. This section will systematically elaborate on the heterogeneity of GSCs and their role in tumorigenesis, the reprogramming of stem cell signaling pathways in *H. pylori*-induced gastric carcinogenesis, as well as the functions of key oncogenes and their mediated signaling axes, aiming to elucidate the core molecular mechanisms underlying GSC/TIC-driven GC progression and provide insights into potential therapeutic targets.

Heterogeneity of GSCs and their role in tumorigenesis. GSCs display considerable heterogeneity across distinct anatomical regions of the stomach. Diverse subpopulations of GSCs can be distinguished by unique molecular markers, distinct functional characteristics and varied responses to pathological stimuli, such as chronic inflammation and *H. pylori* infection. This inherent heterogeneity is of pivotal importance for elucidating the initiation and progression of gastric tumorigenesis. A growing body of research has identified a spectrum of GSC markers, including leucine-rich repeat-containing G-protein-coupled receptor 5 (LGR5), SOX9, cholecystokinin B receptor, MIST1 and Troy. These markers define specific GSC subpopulations that are mainly distributed within antral and corpus glands, with each subpopulation exhibiting differential proliferative activity and differentiation potential (121,122). For example, $LGR5^+$ cells in the antrum are well established as multipotent stem cells with self-renewal and differentiation capabilities, and the expansion of this cell population is closely associated with tumorigenic processes (123). Similarly, SOX9-expressing progenitor cells have been shown to undergo expansion in response to oncogenic insults. Modulation of these $SOX9^+$ cells alters the balance between symmetric and asymmetric cell division, thereby influencing the malignant transformation of gastric epithelial cells (124). Notably, such heterogeneity is not confined to normal GSCs but also extends to CSCs. Gastric CSCs possess self-renewal capacity and tumor-initiating properties, and they notably contribute to intratumoral heterogeneity and therapeutic resistance (125,126).

Under conditions of chronic inflammation and *H. pylori* infection, specific GSC subpopulations acquire tumorigenic potential. *H. pylori* infection induces oxidative stress and activates inflammatory signaling cascades, which in turn alter the stem cell niche and promote malignant transformation. For instance, the bacterial virulence factor CagA triggers the activation of the PI3K/AKT signaling pathway in gastric epithelial cells. This activation leads to the acquisition of CSC-like phenotypes, including upregulated expression of CD44 and enhanced sphere-forming capacity (95). Furthermore, *H. pylori* infection regulates the expression of key transcription factors such as SOX9 through AURKA-mediated cap-dependent translation, which further enhances stemness and facilitates tumorigenesis (127). The inflammatory microenvironment, characterized by cytokines such as IL-17A, also promotes CSC expansion via the IL-17 receptor C (IL-17RC)/NF-κB/NADPH oxidase 1 (NOX1) pathway. This pathway enhances the production of reactive oxygen species and upregulates the expression of stemness-related genes (128). Co-infection with the Epstein-Barr virus can synergistically amplify these effects, inducing structural alterations and promoting proliferation in gastric organoids. This finding underscores the complexity of pathogen interactions in regulating GSC behavior (129).

The fate and function of GSCs are tightly controlled by their microenvironment and intrinsic signaling pathways. Key developmental signaling pathways, including the Wnt/β-catenin and Notch pathways, serve central roles in maintaining stemness and regulating cell fate decisions. The Wnt signaling pathway, which is frequently dysregulated in GC, supports the self-renewal and proliferation of both normal GSCs and gastric CSCs. For example, the Wnt2-SOX4 positive feedback loop has been implicated in sustaining the properties of gastric CSCs and mediating chemoresistance, highlighting the critical role of this pathway in gastric tumor progression (130). The Notch signaling pathway also contributes to the maintenance and differentiation of GSCs, with aberrant activation of this pathway being linked to gastric tumorigenesis (129). The balance between symmetric and asymmetric division of GSCs is modulated by factors such as SOX9 and is influenced by microenvironmental cues. This balance determines the expansion of the GSC pool and the likelihood of malignant transformation (124). In addition, epigenetic regulators and

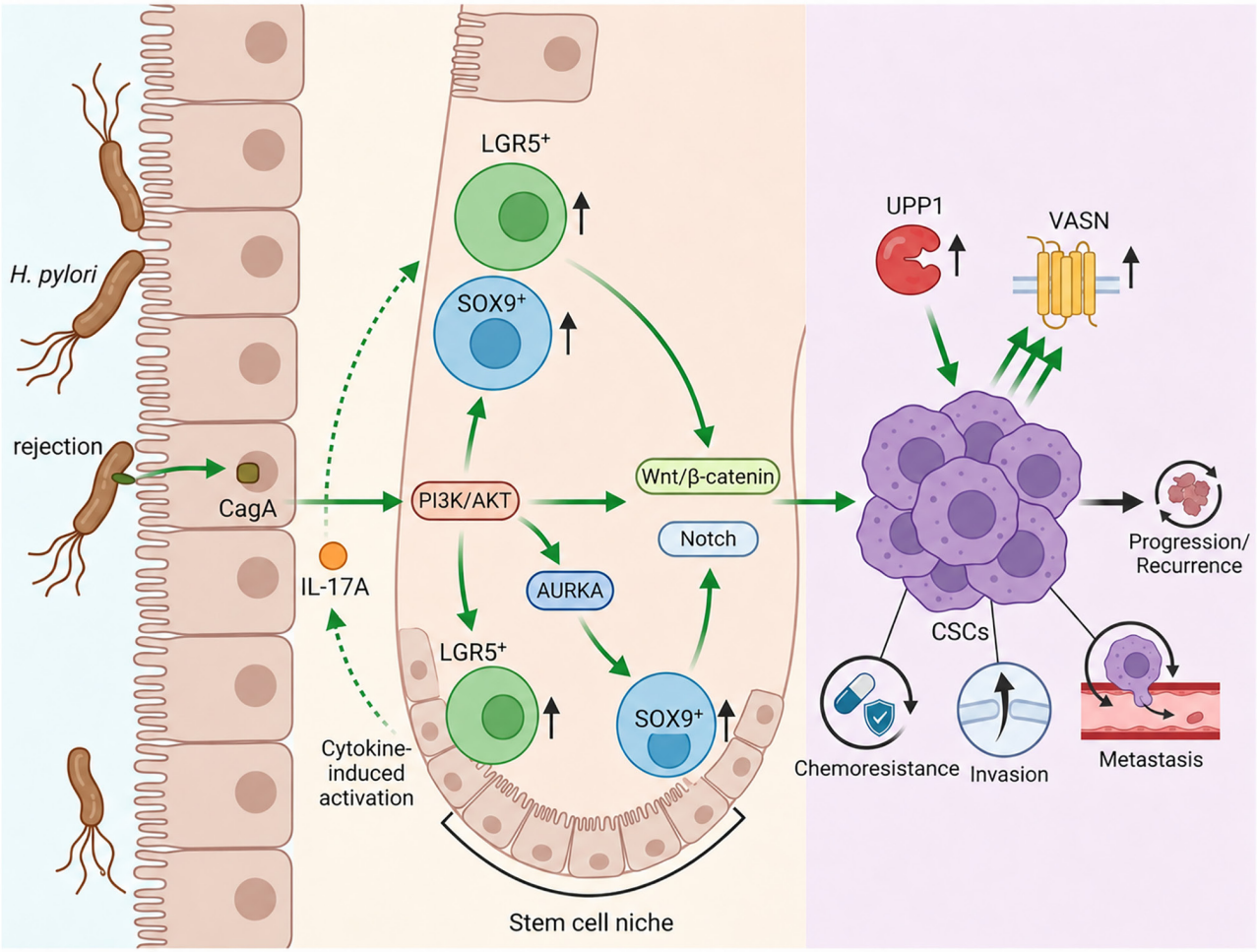

Figure 3. *H. pylori* targets the gastric stem cell niche via CagA/IL-17A. These stimuli activate PI3K/AKT, Wnt/β-catenin and Notch pathways, driving expansion of LGR5$^+$/SOX9$^+$ CSCs. Upregulation of UPP1 and VASN further promotes CSC properties, including chemoresistance, invasion, and metastasis, thereby driving gastric cancer progression and recurrence. *H. pylori*, *Helicobacter pylori*; CSCs, cancer stem cells; UPP1, uridine phosphorylase 1; VASN, vasorin; CagA, cytotoxin-associated gene A; LGR5$^+$, leucine-rich repeat-containing G-protein-coupled receptor 5; AURKA, aurora kinase A.

lncRNAs, including methylated lncRNAs, have emerged as important modulators of stemness and apoptosis resistance in gastric CSCs. These molecules further add layers of complexity to the regulation of GSC fate (131). Mechanistically, epigenetic regulators and lncRNAs modulate GSC fate by regulating gene expression at both transcriptional and post-transcriptional levels (131). DNA/histone-modifying enzymes and RNA methylation regulators can alter chromatin accessibility or RNA stability, thereby affecting genes involved in self-renewal, apoptosis, differentiation and drug resistance (129,131). LncRNAs may recruit chromatin-modifying complexes such as EZH2/PRC2 or LSD1 to silence tumor suppressor or differentiation-related genes, or act as competing endogenous RNAs to sustain stemness-associated pathways, including Wnt/β-catenin, Notch, PI3K/AKT and EMT programs (131). Recent studies further showed that m6A-modified lncRNAs, such as PSMA3-AS1 and MIR22HG, can enhance lncRNA stability, suppress apoptosis and promote gastric CSC stemness through lncRNA-miRNA/protein regulatory axes (129-131). Therefore, these molecules actively contribute to stemness maintenance, apoptosis resistance, and therapeutic resistance in gastric CSCs.

To summarize, the heterogeneity of GSCs, shaped by their spatial localization, molecular identity and interactions with the microenvironment, serves a crucial role in gastric tumorigenesis. Chronic inflammation and *H. pylori* infection induce phenotypic and functional alterations in specific GSC subpopulations, promoting their transformation into CSCs through the activation of oncogenic signaling pathways such as Wnt/β-catenin, Notch and PI3K/AKT (Fig. 3). Understanding the diverse GSC populations and the regulatory networks that govern their fate under pathological conditions provides critical insights into the mechanisms underlying the initiation and progression of GC. This knowledge also offers potential therapeutic targets for the development of novel intervention strategies against GC.

Stem cell signaling pathway reprogramming and tumorigenesis. H. pylori infection exerts a notable impact on the signaling networks of gastric epithelial stem cells, triggering the aberrant activation of pathways that foster epithelial transformation and tumor initiation. Specifically, *H. pylori*-induced oxidative stress and inflammatory responses disrupt the GSC cell niche, thereby inducing the reprogramming of stem cell-associated signaling cascades. For example, *H. pylori* infection enhances the expression of critical stemness regulators such as SOX9 through AURKA-mediated cap-dependent

translational control, which in turn augments the proliferation and malignant transformation of gastric epithelial cells (127). Additionally, IL-17A, whose levels are elevated in *H. pylori*-associated GC, contributes to the acquisition of cancer stem cell properties by activating the IL-17RC/NF-κB/NOX1 signaling axis. This activation leads to increased reactive oxygen species production and upregulation of stemness-related genes, ultimately facilitating tumorigenesis (128). Co-infection with Epstein-Barr virus further amplifies these pathogenic effects by stimulating proliferation and morphogenetic alterations in gastric organoids, suggesting a synergistic role of dual pathogens in perturbing stem cell signaling pathways (129). Long-term *H. pylori* infection also drives gastric epithelial cells toward a CSC-like differentiation program via TGFβ-dependent mechanisms, which are mediated by *H. pylori*-activated gastric fibroblasts. This finding highlights the crucial involvement of the TME in regulating stem cell fate during gastric carcinogenesis (132).

At the molecular level, transcription factors including SOX9 are modulated by upstream signaling events, such as AURKA activation and the WNT2-SOX4 feedback loop. These regulatory mechanisms sustain the stemness and tumorigenic potential of gastric stem cells under *H. pylori* infection (127,130). Moreover, CSC markers such as LGR5 and aquaporin-5 (AQP5) have been identified as key determinants of gastric CSC fate. Notably, AQP5 promotes autophagic activity through unc-51-like autophagy-activating kinases 1 ubiquitination, which is essential for maintaining CSC stemness and tumorigenic capacity (133). The crosstalk between these signaling pathways and stem cell markers forms a complex regulatory network, wherein *H. pylori* infection mediates stem cell signaling reprogramming to facilitate malignant transformation. This reprogramming process is further fine-tuned by epigenetic and post-transcriptional regulatory mechanisms, including N6-methyladenosine (m6A) methylation of lncRNAs. Such modifications stabilize transcripts associated with stemness maintenance and apoptosis suppression, thereby driving the progression from precancerous lesions to malignant tumors (131). Collectively, these findings clarify the mechanisms by which *H. pylori*-induced aberrant activation and reprogramming of stem cell signaling pathways promote epithelial transformation and gastric tumorigenesis, providing potential therapeutic targets for clinical intervention.

Epigenetic modifications serve a pivotal role in orchestrating stem cell fate decisions during gastric carcinogenesis. Site-specific methylation of lncRNAs, such as PSMA3-AS1 and MIR22HG, enhances their stability. These modified lncRNAs subsequently suppress apoptosis and promote stemness in GC stem cells through miRNA/protein regulatory axes, thereby facilitating tumor development (131). Additionally, m6A modifications mediated by reader proteins such as insulin-like growth factor 2 mRNA-binding protein 2 stabilize transcripts (such as colony stimulating factor 2) in mesenchymal stem cells (MSCs). This stabilization reprograms MSCs into cancer-promoting phenotypes that support tumor progression (134). These epigenetic alterations modulate the expression of key stemness regulators, including spalt like transcription factor 4 and long intergenic non-protein coding RNA, regulator of reprogramming. The interaction between these regulators is associated with tumor aggressiveness and *H. pylori* infection status, indicating a direct link between infection-driven epigenetic reprogramming and malignant transformation (135). Furthermore, transcription factors such as KH-type splicing regulatory protein and nucleoside diphosphate kinase 2 are involved in maintaining CSC properties through epigenetic regulatory mechanisms, thereby promoting the proliferation, migration and survival of GC cells (136,137). The dynamic epigenetic landscape regulates the plasticity of gastric epithelial cells, enabling the transition from normal stem cells to malignant CSCs under the influence of *H. pylori*-induced inflammation and microenvironmental cues (138). Elucidating these epigenetic mechanisms offers promising strategies for targeting stem cell fate decisions to prevent the progression of precancerous lesions to GC.

H. pylori infection induces aberrant activation and epigenetic reprogramming of stem cell signaling pathways, which collectively promote epithelial transformation and gastric tumorigenesis (Fig. 3). The integration of inflammatory signaling, transcriptional regulation and epigenetic modifications orchestrates the alteration of stem cell fate that drives malignant progression. Targeting these reprogrammed pathways and epigenetic regulators holds notable potential for the development of novel therapeutic strategies to intercept the initiation and progression of GC.

Key oncogenes and their functions. Uridine phosphorylase 1 (UPP1) has been increasingly recognized as a pivotal oncogene in GC progression, particularly in the context of *H. pylori infection*. Single-cell RNA sequencing analyses of gastric mucosal biopsies spanning the pathological spectrum from non-atrophic gastritis to early GC have demonstrated a gradual upregulation of UPP1 expression, which exhibits a positive association with malignant transformation (139). This elevated UPP1 expression is, at least partially, driven by *H. pylori* infection through activation of the NF-κB signaling pathway which is a well-established mediator of inflammatory responses and oncogenic processes (139). Functionally, upregulated UPP1 enhances the proliferation and migration of GC cells, which are two core hallmarks of cancer progression. Additionally, UPP1-related pathways, such as the macrophage migration inhibitory factor pathway, modulate the TME, further facilitating tumor growth and immune evasion. Cumulative evidence thus positions UPP1 as a driver of malignant progression in GC, bridging chronic infection-induced inflammation with oncogenic signaling cascades. This insight underscores the potential of UPP1 as a biomarker for early detection and a therapeutic target to interrupt the progression of *H. pylori*-associated gastric malignancies (139).

Beyond UPP1, several other oncogenes, including MYB proto-oncogene like 2 (MYBL2), nuclear receptor-related 1 protein (Nurr1) and protogenin (PRTG), have been implicated in *H. pylori*-mediated gastric carcinogenesis. *H. pylori* infection markedly upregulates MYBL2 expression via activation of STAT3, which in turn promotes NF-κB activation to establish a pro-tumorigenic microenvironment. MYBL2 enhances cellular proliferation and migration and its downregulation has been shown to inhibit *in vivo* tumor growth, highlighting its oncogenic role in GC progression (140). Similarly, the orphan nuclear receptor Nurr1 is upregulated in GC and is induced by *H. pylori* infection through the PI3K/AKT-Sp1 pathway. Nurr1

directly upregulates CDK4 expression, thereby facilitating cell cycle progression and tumor proliferation in both *in vitro* and *in vivo* models (141). Another oncogenic protein, PRTG, is transcriptionally upregulated by *H. pylori* through stabilization of the transcription factor zinc finger E-box-binding homeobox 1, which activates the cGMP/protein kinase G (PKG) signaling pathway. This signaling axis promotes proliferation, metastasis and chemoresistance in GC cells; notably, pharmacological inhibition of PKG synergizes with chemotherapeutic agents to suppress tumor growth (142). Collectively, these oncogenes illustrate the diverse molecular mechanisms through which *H. pylori* infection drives gastric carcinogenesis by progressively upregulating genes that augment malignant phenotypes.

Furthermore, growing attention has been paid to the role of ncRNAs including circRNAs and lncRNAs in regulating the expression of genes associated with cellular proliferation and migration. For example, circ_0075829 is upregulated in *H. pylori*-infected GC cells, where it promotes proliferation and invasion by sponging miR-149-5p and regulating argonaute RISC component 1 expression (143). LncRNAs such as H19 are also induced by *H. pylori* CagA, contributing to the DNA damage response and enhanced malignancy (144). These findings suggest a complex regulatory network involving both coding and non-coding genes that collectively drive GC progression.

In summary, UPP1 and other key oncogenes are progressively upregulated during gastric carcinogenesis, particularly under the influence of *H. pylori* infection. Their roles in promoting cellular proliferation, migration and survival highlight their importance as potential biomarkers and therapeutic targets for intercepting the malignant transformation process in GC.

The VASN-COL4A1-PI3K/AKT signaling axis serves as a critical molecular pathway mediating gastric tumorigenesis in the setting of *H. pylori* infection. VASN, a transmembrane glycoprotein, has been identified as being markedly upregulated in GC tissues and closely associated with adverse clinical outcomes (96). Notably, *H. pylori* infection induces VASN expression via HIF-1α, which itself is upregulated in response to the chronic inflammatory and hypoxic microenvironment elicited by the infection. A functional study has demonstrated that VASN overexpression promotes the proliferation, migration and invasion of gastric epithelial cells, whereas VASN knockdown suppresses these malignant phenotypes, highlighting its oncogenic role (96).

Mechanistically, VASN exerts its tumor-promoting effects by regulating COL4A1, a key component of the ECM (96,145). Acting downstream of VASN, COL4A1 activates the PI3K/AKT signaling pathway, a canonical oncogenic cascade that governs cellular growth, survival and motility (96,145). Activation of PI3K/AKT signaling via the VASN-COL4A1 axis facilitates tumor progression by enhancing cellular proliferation and migration, processes essential for cancer invasion and metastasis (96,145). This axis thus integrates ECM remodeling with intracellular oncogenic signaling, linking *H. pylori*-induced environmental alterations to intracellular pathways driving carcinogenesis (96,145). Supporting this, integrative bioinformatics analyses of *H. pylori*-associated stomach adenocarcinoma have identified COL4A1 as one of the hub genes that are epigenetically deregulated and upregulated in infected tissues. Experimental infection of gastric epithelial cells with *H. pylori* induces COL4A1 expression, which is associated with increased proliferation, colony formation and migration. Silencing of COL4A1 markedly attenuates these malignant phenotypes, underscoring its functional importance in *H. pylori*-driven GC progression (145).

The VASN-COL4A1-PI3K/AKT axis is further interconnected with other oncogenic pathways activated by *H. pylori* infection, including STAT3 and NF-κB signaling, which collectively contribute to the formation of a pro-tumorigenic microenvironment. This axis also exemplifies how bacterial infection can modulate host gene expression and signaling networks to promote tumor development (Fig. 3). Due to its central role in gastric tumorigenesis, this pathway represents a promising therapeutic target. Inhibiting components of the VASN-COL4A1-PI3K/AKT axis may disrupt the oncogenic signaling cascade initiated by *H. pylori* infection, thereby impeding tumor growth and progression. The VASN-COL4A1-PI3K/AKT signaling axis is therefore a crucial mediator of *H. pylori*-induced GC progression. By linking infection-induced hypoxia and ECM remodeling to intracellular oncogenic signaling, this pathway highlights the complex interplay between microbial factors and host cellular mechanisms in gastric carcinogenesis. Targeting this axis offers a potential strategy for therapeutic intervention in *H. pylori*-associated GC.

5. Diagnostic biomarkers and therapeutic strategies from a clinical perspective

H. pylori infection is the primary etiological factor of GC, contributing to ~76% of global GC cases (1-5). The clinical management of *H. pylori*-associated GC remains challenged by late diagnosis, worse prognosis and limited efficacy of conventional therapies, highlighting the urgent need for precision-oriented diagnostic and therapeutic approaches (1,5). Biomarkers have evolved from research tools to critical guides for clinical decision-making, enabling early detection, prognostic stratification and personalized treatment selection in GC. Concurrently, advances in targeted therapy, immunotherapy, microecological regulation and nanotechnology have opened new avenues for interrupting *H. pylori*-driven carcinogenesis and improving treatment outcomes. The present section systematically reviews the clinical application of molecular biomarkers in early diagnosis and prognosis evaluation of *H. pylori*-associated GC, and further discusses the latest progress in targeted therapy, immunotherapy, microecological regulation and nanotechnology-assisted therapy, aiming to provide a comprehensive overview of the current landscape and future directions for clinical management of this disease (Fig. 4).

Application of molecular biomarkers in early diagnosis and prognostic evaluation. Early detection and precise prognostic assessment of GC continue to pose notable challenges, primarily attributable to the molecular heterogeneity of the disease and the frequent occurrence of late clinical manifestations. Molecular biomarkers, especially ncRNAs such as lncRNAs and miRNAs, have emerged as promising tools for non-invasive diagnosis and prognosis. This is largely

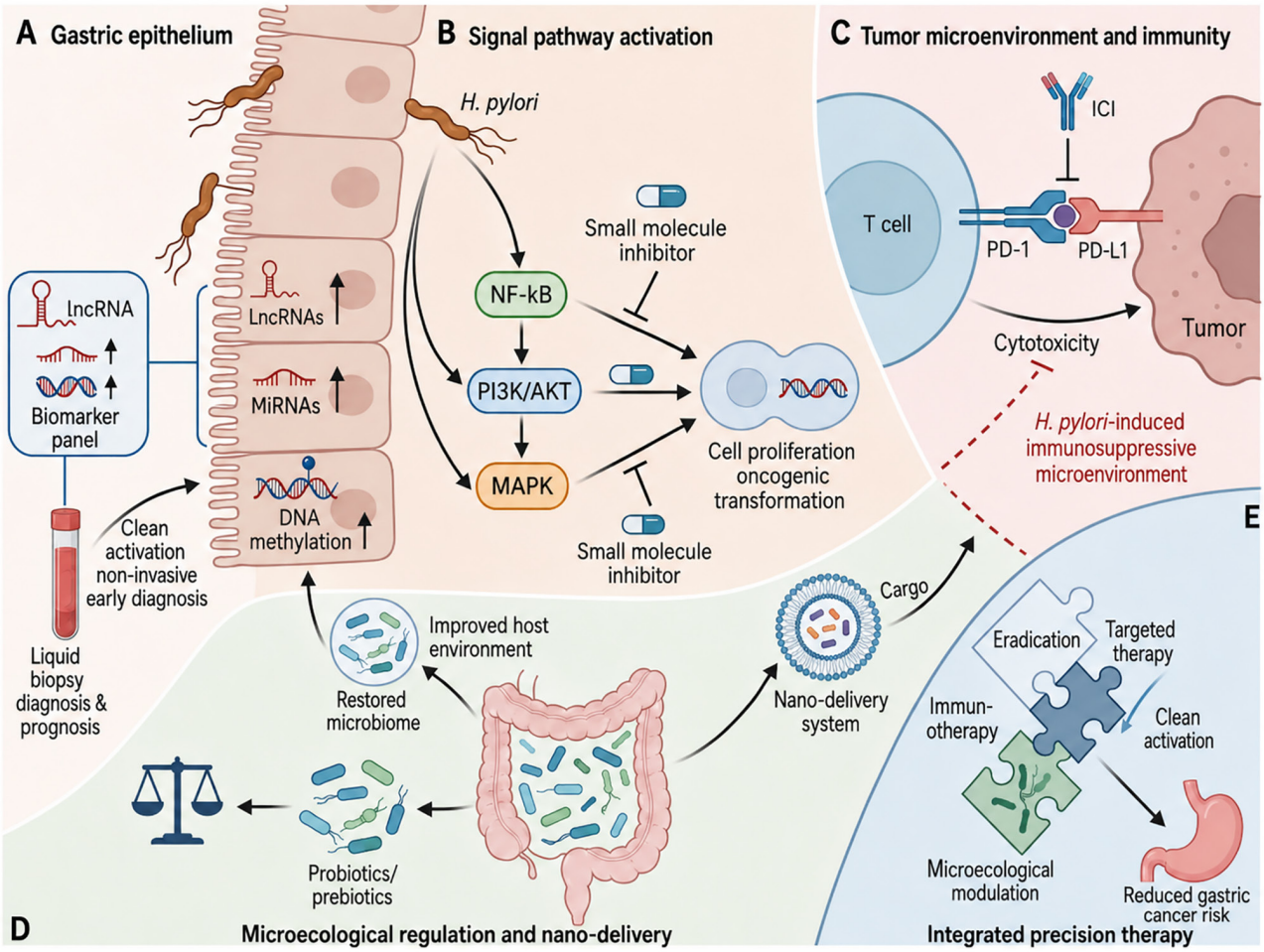

Figure 4. Clinical diagnostic and therapeutic strategies for *H. pylori*-associated gastric cancer. (A) Liquid biopsy-based biomarkers (such as lncRNAs, miRNAs and DNA methylation) enable non-invasive early diagnosis. (B) Targeting oncogenic pathways (NF-κB, PI3K/AKT and MAPK) with small-molecule inhibitors blocks cell transformation. (C) ICIs restore T cell cytotoxicity in the immunosuppressive tumor microenvironment. (D) Microbiota modulation and nano-delivery systems improve therapeutic efficacy. (E) Integrated precision therapy reduces gastric cancer risk. *H. pylori*, *Helicobacter pylori*; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; lncRNAs, long non-coding RNA; miRNA, microRNA; ICI, immune checkpoint inhibitors.

due to their pivotal regulatory roles in gene expression and tumorigenic processes. Among lncRNAs, H19 and GClnc1 have been found to be markedly upregulated during *H. pylori*-associated gastric carcinogenesis. These lncRNAs drive tumor progression by modulating oncogenic signaling pathways, as well as promoting cancer cell proliferation, migration and invasion. For example, H19 functions as a molecular sponge sequestering tumor-suppressive miRNAs, thereby augmenting oncogene expression. By contrast, GClnc1 exerts its effects by influencing chromatin remodeling and inflammation-related pathways that are crucial to GC pathogenesis (146). Similarly, miRNAs including miR-155 and miR-7 have been validated as potential non-invasive biomarkers. Specifically, miR-155 expression is elevated in both gastric tissues and serum samples from *H. pylori*-infected patients with chronic gastritis. Notably, this upregulation is independent of bacterial virulence factors such as CagA and VacA, suggesting that miR-155 could serve as a marker for early inflammatory lesions that precede malignant transformation (147). Additionally, miR-7 has been implicated in the regulation of key signaling cascades involved in the malignant transformation of gastric epithelial cells (147). The detection of these miRNAs in serum or other bodily fluids thus provides a minimally invasive approach for early GC diagnosis and monitoring of disease progression.

Apart from ncRNAs, the expression patterns of bile acid receptors have been associated with GC subtypes and patient prognosis, laying a molecular foundation for precision medicine. Aberrations in bile acid receptor expression modulate the TME and cellular signaling pathways, thereby impacting tumor behavior and therapeutic responsiveness. For instance, differential expression of receptors such as farnesoid X receptor and G protein-coupled bile acid receptor 1 has been associated with distinct molecular subtypes of GC. This association may facilitate therapeutic decision-making and prognostic stratification (148). Integrating bile acid receptor profiling with established molecular markers enhances the granularity of GC classification, thereby promoting the development of personalized treatment strategies.

Other molecular biomarkers, including protein-coding genes and their associated signaling pathways, complement the current landscape of diagnostic and prognostic indicators. For example, low-density lipoprotein receptor-related protein 8 is upregulated in *H. pylori*-infected gastric tissues and CSCs. This upregulation promotes nuclear translocation of β-catenin,

which enhances the transcriptional activity of genes linked to tumor progression and chemoresistance (149). Similarly, overexpression of neural precursor cell expressed, developmentally downregulated 9 and downregulation of forkhead box L1 have been associated with a worse prognosis in intestinal-type GC, and these expression patterns are associated with advanced disease stage and metastasis (150). Together with ncRNAs, these markers form a multi-dimensional biomarker panel that may improve the accuracy of early detection and prognostic evaluation.

Advances in bioinformatics and high-throughput sequencing technologies have facilitated the identification of novel biomarker panels. For example, the combination of AURKA, centrosomal protein 55, denticleless E3 ubiquitin protein ligase homolog and TTK protein kinase genes exhibits high sensitivity and specificity in distinguishing malignant gastric tissues from normal ones, thereby enhancing early GC detection (151). Furthermore, liquid biopsy techniques that incorporate circulating miRNAs and methylation markers, such as miR-148a methylation, have shown promise in diagnosing gastric indefinite dysplasia, a precancerous lesion (152). These approaches offer less invasive, repeatable and dynamic monitoring tools, which are essential for early clinical intervention.

Notably, the molecular heterogeneity of GC necessitates the adoption of integrated biomarker strategies that combine lncRNAs, miRNAs, protein-coding genes and receptor expression profiles. Such integration enables comprehensive capture of the complex pathogenic processes influenced by *H. pylori* infection and host factors, thereby enhancing diagnostic precision and prognostic evaluation and facilitating the development of tailored therapeutic strategies. Continued validation of these biomarkers in large, diverse patient cohorts and the development of standardized detection platforms are critical for their successful clinical translation. Ultimately, molecular biomarkers hold substantial potential to transform the early diagnosis and prognosis of GC, improving patient outcomes through the implementation of personalized medicine.

Advances in targeted therapy and immunotherapy. The molecular mechanisms underlying GC development driven by *H. pylori* infection are characterized by the dysregulation of multiple critical signaling pathways. Among these, the NF-κB and PI3K/AKT pathways stand out as key mediators, as their aberrant activation fosters chronic inflammation, aberrant cell proliferation and enhanced cell survival, all of which contribute to the initiation and progression of tumorigenesis. Targeted therapeutic strategies focusing on these dysregulated pathways have thus emerged as promising approaches to interrupt the cascade of *H. pylori*-driven carcinogenesis. For example, multi-omics profiling has facilitated the identification of hub genes involved in immune modulation and inflammatory responses, such as C-X-C motif chemokine ligand 1 and STAT4. Notably, these hub genes have been shown to interact with clinically approved drugs, indicating their potential as actionable targets for precision medicine in *H. pylori*-associated GC (16). Additionally, the ERK/MMP9 signaling cascade has been implicated in promoting GC cell invasion and metastasis; this cascade is activated by *H. pylori*-induced upregulation of semaphorin 5A. Pharmacological inhibition of ERK or MMP9 has been demonstrated to attenuate these malignant phenotypes, highlighting these molecules as novel molecular targets for therapeutic intervention (153). Moreover, the tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein ε (YWHAE) gene, which is involved in ferroptosis regulation and is modulated by *H. pylori* infection, intersects with multiple oncogenic signaling pathways, including MAPK, NF-κB and PI3K. Small-molecule compounds targeting YWHAE-related signaling cascades have been proposed, thereby expanding the arsenal of potential targeted agents (154). Collectively, these findings underscore the feasibility of developing pathway-specific inhibitors that block *H. pylori*-activated oncogenic signaling, offering a more personalized and effective therapeutic paradigm for GC management beyond conventional chemotherapy.

ncRNAs have been increasingly recognized as pivotal regulators of gene expression during *H. pylori*-related gastric carcinogenesis. These ncRNAs modulate a spectrum of biological processes, including inflammatory responses, immune cell function and tumor progression. A previous review article emphasized the central role of ncRNAs in orchestrating the inflammatory TME and regulating immune responses during *H. pylori* infection, suggesting their potential utility as both diagnostic biomarkers and therapeutic targets (155). For instance, dysregulated expression of specific miRNAs and lncRNAs has been shown to alter the production of key inflammatory cytokines and the expression of immune checkpoint molecules, thereby influencing tumor immune evasion and disease progression. Therapeutic strategies aimed at restoring the normal expression of dysregulated ncRNAs or inhibiting aberrantly upregulated ncRNAs hold promise for reprogramming the TME to a more antitumorigenic state and enhancing antitumor immune responses. The integration of ncRNA-based therapeutic approaches with existing treatment modalities is anticipated to improve early diagnosis, refine prognostic assessment and advance personalized therapy for *H. pylori*-associated GC. These molecular interventions represent a novel frontier in targeted therapy, leveraging the regulatory capabilities of ncRNAs to disrupt the pathogenic signaling cascades triggered by *H. pylori* infection.

Immunotherapy has evolved into an indispensable therapeutic modality for GC, with immune checkpoint inhibitors such as anti-PD-1/PD-L1 antibodies demonstrating notable clinical efficacy (9). However, the influence of *H. pylori* on immunotherapy is not merely associative. Mechanistically, *H. pylori* infection reshapes the tumor immune microenvironment by upregulating immune checkpoint molecules such as PD-L1, impairing dendritic cell maturation and antigen presentation, promoting the accumulation of immunosuppressive cell populations including regulatory T cells, myeloid-derived suppressor cells and tumor-associated macrophages, and reducing the infiltration and cytotoxic activity of $CD8^+$ T cells (111,156-165). In addition, infection-associated inflammatory and metabolic reprogramming, including increased secretion of IL-6, IL-10 and VEGF as well as lactate accumulation, further reinforces T cell dysfunction and immune escape (166-169). Through these mechanisms, *H. pylori* may diminish the efficacy of immune checkpoint inhibitors in some patients. Nevertheless, current evidence remains heterogeneous, and the impact of *H. pylori*

on immunotherapeutic responses may vary according to tumor subtype, host immune context and microbial background. This complexity underscores the critical need for a comprehensive understanding of the role of *H. pylori* in immune regulation to optimize immunotherapeutic outcomes. Vaccine development targeting *H. pylori* virulence factors remains an active area of research, with the goal of preventing infection and subsequent carcinogenesis. Recent advances in this field include the application of artificial intelligence-driven design to develop multiepitope vaccines tailored to diverse *H. pylori* subtypes, an innovation that may revolutionize preventive strategies and enhance immunotherapeutic responses (170). Additionally, DNA vaccines encoding *H. pylori* antigens have exhibited immunotherapeutic potential by stimulating T cell-mediated immune responses and remodeling the TME to favor antitumor immunity (171). Novel immunomodulatory agents, such as bispecific antibodies that simultaneously target immune checkpoints and angiogenic factors (such as CD47 and VEGF), have demonstrated synergistic antitumor effects in preclinical GC models (172). Taken together, these advances in immunotherapy, when combined with targeted therapies and vaccine-based strategies, offer a holistic approach to enhancing host antitumor immunity against *H. pylori*-driven gastric carcinogenesis and improving clinical outcomes for patients with this malignancy.

Microecological regulation and nanotechnology-assisted therapy. The intricate relationship between *H. pylori* infection, gastric carcinogenesis and the gut microbiota has increasingly highlighted the importance of microecological regulation in preventing and treating *H. pylori*-associated GC. Dysbiosis of the gastric and intestinal microbiota induced by *H. pylori* infection disrupts the microbial balance, promoting tumorigenic processes through inflammation, immune modulation and alteration of the TME (173). Restoration of microecological balance by modulating the gastrointestinal microbiota emerges as a promising strategy to suppress tumor-promoting factors and enhance host immunity. This approach involves the use of probiotics, prebiotics and natural compounds that can selectively inhibit pathogenic bacteria while promoting beneficial microbes, thereby re-establishing homeostasis within the gastric niche. For instance, berberine, a natural isoquinoline alkaloid derived from medicinal herbs such as *Coptidis rhizoma*, has demonstrated potent antimicrobial activity against *H. pylori* and beneficial effects on gut microbiota composition. Beyond its antimicrobial properties, berberine exerts multifaceted anticancer effects including inhibition of cancer cell proliferation, induction of apoptosis and modulation of the TME and gut microbiota, which collectively contribute to its therapeutic potential in GC (174,175).

However, the clinical translation of such bioactive compounds is often limited by poor bioavailability and stability in the harsh gastric environment. Nanotechnology offers innovative solutions to these challenges by enabling precise delivery and controlled release of antimicrobial and anticancer agents directly to the gastric mucosa. Nanomaterials can be engineered to protect drugs from gastric acidity, enhance mucosal penetration and target specific bacterial virulence factors such as urease and vacuolating cytotoxin A, thereby improving eradication rates of *H. pylori* and reducing antibiotic resistance (176). Additionally, nanocarriers facilitate the co-delivery of multiple agents, including natural compounds like berberine, to synergistically inhibit tumor progression and restore microecological balance. For example, nanotechnology-enabled TME reprogramming can modulate immune responses and microbiota dysbiosis, enhancing the efficacy of immunotherapy in *H. pylori*-associated GC (173). Despite these advances, challenges remain in optimizing nanomaterial design to achieve precise targeting, minimize off-target effects and overcome potential toxicity. Continued refinement and integration of nanotechnological strategies with microecological modulation hold great promise for developing effective, targeted therapies that address both the microbial and tumorigenic components of *H. pylori*-related GC. This multidisciplinary approach represents a frontier in precision medicine, aiming to improve clinical outcomes through restoration of microbial homeostasis and enhanced drug delivery systems (Fig. 4). Recent studies on exosome-mediated mechanisms, H. pylori-related immunotherapy and bacteria-mediated cancer therapy further support this integrated therapeutic direction (177-179).

6. Conclusions

The present review highlights the central role of *H. pylori* infection as the primary driver of gastric carcinogenesis through a coordinated network of virulence factors, oncogenic signaling pathways and host regulatory mechanisms. The bacterial virulence factors CagA and VacA act as key upstream regulators that disrupt epithelial integrity, induce chronic inflammation and activate multiple oncogenic cascades, including NF-κB, MAPK, JAK/STAT, PI3K/AKT and Hippo-YAP signaling pathways. A major conceptual advance is the recognition that gastric carcinogenesis is not solely driven by direct bacterial effects but rather represents a multifactorial process involving dynamic interactions between *H. pylori*, the host immune system, gastric microbiota and the TME. *H. pylori*-induced immune modulation, including immune checkpoint activation and recruitment of immunosuppressive cell populations, plays a crucial role in establishing a tumor-permissive microenvironment. Epigenetic dysregulation, particularly DNA methylation and ncRNA-mediated regulation, constitutes another critical layer linking chronic infection to malignant transformation. These changes can persist even after bacterial eradication, thereby contributing to residual cancer risk. Furthermore, the reprogramming of GSCs and the acquisition of CSC-like properties represent key events in tumor initiation and progression. These processes are driven by the integration of inflammatory signaling, oncogenic pathway activation and microenvironmental cues. From a clinical perspective, emerging molecular biomarkers, including ncRNAs, epigenetic markers and oncogene signatures, hold promise for improving early detection and prognostic stratification. At the same time, advances in targeted therapy and immunotherapy offer new opportunities for disrupting *H. pylori*-driven oncogenic signaling networks. However, the therapeutic response remains heterogeneous, underscoring the need for more precise and individualized treatment strategies.

7. Future perspectives

Despite notable progress in understanding *H. pylori*-mediated gastric carcinogenesis, several critical challenges remain. First, the majority mechanistic insights are derived from *in vitro* systems and animal models, which may not fully recapitulate the complexity and heterogeneity of the human gastric microenvironment. Future studies should prioritize well-designed longitudinal and multi-center clinical investigations to validate these findings in real-world patient populations. Second, the intricate interactions among *H. pylori*, non-*Helicobacter* microbiota and host immune responses remain incompletely understood. In particular, the precise roles of microbial metabolites, interspecies interactions and spatial organization of microbial communities in tumor development require further elucidation. Advanced technologies such as single-cell sequencing, spatial transcriptomics and multi-omics integration are expected to provide deeper insights into these complex networks. Third, although numerous molecular biomarkers have been proposed, their clinical translation is still limited by a lack of standardization, insufficient validation and variability across populations. Future research should focus on establishing robust, reproducible biomarker panels and integrating them into clinically applicable diagnostic platforms. Fourth, the impact of *H. pylori* infection on therapeutic responses, particularly immunotherapy, remains controversial. A more comprehensive understanding of how microbial status influences immune checkpoint signaling and tumor immune microenvironment is essential for optimizing treatment strategies and patient selection. In addition, emerging therapeutic approaches, including microbiome modulation, vaccine development and nanotechnology-assisted drug delivery, offer promising avenues for intervention. However, their efficacy, safety and long-term outcomes require further rigorous evaluation in clinical settings. Overall, future research should aim to integrate molecular mechanisms, microbial ecology and clinical data to develop precision medicine strategies for the prevention, early detection and treatment of *H. pylori*-associated GC.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

TD participated in writing the original draft, literature collection and review. WH contributed to writing the original draft, literature collection and review, and visualization. XQ was involved in reviewing and editing, and literature collection and review. YZ performed reviewing and editing, project administration and visualization. HW participated in reviewing and editing, conceptualization, supervision and project administration. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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