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Helicobacter pylori and gastric cancer: mechanisms and new perspectives

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Abstract

Gastric cancer remains a significant global health challenge, with Helicobacter pylori (*H. pylori*) recognized as a major etiological agent, affecting an estimated 50% of the world's population. There has been a rapidly expanding knowledge of the molecular and pathogenetic mechanisms of *H. pylori* over the decades. This review summarizes the latest research advances to elucidate the molecular mechanisms underlying the *H. pylori* infection in gastric carcinogenesis. Our investigation of the molecular mechanisms reveals a complex network involving STAT3, NF-κB, Hippo, and Wnt/β-catenin pathways, which are dysregulated in gastric cancer caused by *H. pylori*. Furthermore, we highlight the role of *H. pylori* in inducing oxidative stress, DNA damage, chronic inflammation, and cell apoptosis—key cellular events that pave the way for carcinogenesis. Emerging evidence also suggests the effect of *H. pylori* on the tumor microenvironment and its possible implications for cancer immunotherapy. This review synthesizes the current knowledge and identifies gaps that warrant further investigation. Despite the progress in our previous knowledge of the development in *H. pylori*-induced gastric cancer, a comprehensive investigation of *H. pylori*'s role in gastric cancer is crucial for the advancement of prevention and treatment strategies. By elucidating these mechanisms, we aim to provide a more in-depth insights for the study and prevention of *H. pylori*-related gastric cancer.

Keywords *H. Pylori*, Gastric cancer, Mechanism, Signaling pathway

Introduction

Gastric cancer, one of the most common cancers six decades ago all over the world [1], has experienced a decline in incidence and mortality over recent years [2]. However, it is still the fifth most common cancer and the fifth leading cause of cancer-related fatalities in the world, according to the GLOBOCAN 2022 [3]. Gastric cancer has a complex etiology, involving environmental, genetic, and microbial factors implicated in its pathogenesis. Among these, Helicobacter pylori (*H. pylori*) stands out as a major risk factor for gastric cancer [4], with numerous studies confirming the role of this bacterium in the multistep process of gastric tumorigenesis, as put forward by Correa's cascade [5]. In 1988, Correa initially proposed a disease model elucidating the malignant transformation from *H. pylori* infection to gastric cancer, involving the development of chronic atrophic gastritis following persistent inflammatory stimulation. Subsequent intestinal metaplasia could gradually progress to precancerous lesion, finally leading to gastric adenocarcinoma [6].

In 1982, Robin Warren and Barry Marshall made a groundbreaking discovery by isolating a spiral-shaped

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bacterium from the mucosal samples of gastritis and peptic ulcer patients [7]. This bacterium was eventually identified as *H. pylori*, a finding that challenged the long-standing belief that the stomach was sterile. Marshall further provided the proof of causality for *H. pylori* to cause gastric disease and cure of this disease following the eradication of *H. pylori*, thus fulfilling the Koch's postulates [8]. These findings provided direct evidences that gastric disease was attributable to *H. pylori* infection. Eventually, in 2005, Warren and Marshall were awarded the Nobel Prize in Physiology or Medicine [9].

To further understand the function of *H. pylori* in gastric carcinogenesis, Correa proposed a model for intestinal gastric cancer in 1992, identifying *H. pylori* infection as the initiating contributor involved in gastric carcinogenesis [10]. This model highlighted the bacterium's role in the development of gastric cancer. The International Agency for Research on Cancer (IARC) classified *H. pylori* as a Group 1 carcinogen in 1994 [11], emphasizing the urgent need for effective diagnostic and treatment strategies. The discovery of *H. pylori* has not only clarified the pathogenesis of gastric diseases, but also revolutionized the treatment of these diseases, significantly improved the global health (Table 1).

To explore the new approaches to enhance the efficacy of *H. pylori*, a more comprehensive understanding of the molecular mechanisms by which *H. pylori* interacts with the host to facilitate gastric cancer development is crucial. Overall, this review is necessary as it will help us to pay more attention to the latest advances on the virulence and pathological mechanisms of *H. pylori*.

Epidemiology

The human stomach serves as the exclusive natural reservoir for *H. pylori*. Evidence suggests that *H. pylori* appears to have spread from east Africa about 58,000 years ago [12]. As an ancient microorganism, *H. pylori* is widespread, with an estimated 50% of the global population carrying this bacterium [13]. Notably, most newly *H. pylori* infections are acquired in childhood, often before the age of 10. Once an individual is infected with *H. pylori*, this pathogen typically persists for life [14]. The transmission routes of *H. pylori* are believed to involve fecal-oral, gastric-oral, and oral-oral pathways, with person-to-person and contaminated water transmission regarded as the primary modes in developing countries [15, 16].

A significant decrease in *H. pylori* prevalence has occurred in recent years. From 2015 to 2022, the prevalence of *H. pylori* infection among adults has declined from 50–55–43.9% in the world [17]. This reduction is attributed to factors such as improved socioeconomic status, enhanced sanitation and hygiene practices, and eradication therapy [18]. However, the prevalence among children and adolescents remains high at 35.1% during the same period [19, 20]. Significant geographical heterogeneity still exists, with the highest prevalence rate found in Africa (79.1%), followed by Latin America and the Caribbean (63.4%), and Asia (54.7%), while the relative lower rates found in Northern America (37.1%) and Oceania (24.4%) [4].

In general, the epidemiological characteristics of *H. pylori* infection are multifaceted, with variations influenced by age, geographic location, ethnicity, socioeconomic factors, living standards, and hygiene conditions

Table 1 Key milestones in the understanding of *H. Pylori* and gastric carcinogenesis

Timeline	Events
1982	*H. pylori* was discovered by Marshall and Warren
1988	Correa's cascade was firstly proposed
1989	*H. pylori* was renamed from Campylobacter pylori
1990	*H. pylori* caused duodenal ulcer, and the eradication cured duodenal ulcer
1991	New gastritis classification system (Sydney system) was established
1992	Gastric mucosa-associated lymphoid tissue lymphoma was cured by *H. pylori* eradication
1994	*H. pylori* was classfied as a class I carcinogen by WHO
1996	Updated gastritis classification of Sydney-Houston system
1999	PPI-based triple therapy for *H. pylori* eradication
2000	Maastricht II Consensus Report recommends *H. pylori* testing and treatment in adult patients
2001	*H. pylori* was proved as a key factor in gastric carcinogenesis
2004	*H. pylori* eradication for gastric cancer prevention
2005	Nobel prize for Marshall and Warren
2012	Management of precancerous lesions in the stomach guidelines
2015	Kyoto Gastritis Consensus defines *H. pylori*-associated gastritis as infectious disease
2019	Taipei consensus about implementation of screening and treatment strategies for gastric cancer prevention
2021	*H. pylori* was again identified as a human carcinogen by the U.S. Department of Health and Human Services in the 15th Report on Carcinogens

[20]. Understanding these dynamics is critical to developing effective public health strategies to reduce the global burden of *H. pylori*-related gastric cancer.

Genomic characteristics of *H. Pylori*

The *H. pylori* genome has a high level of genetic plasticity and extensive geographic variation, intricately linked to its ability of colonization in human stomach and induce gastric disease [21]. This highly heterogeneous bacterium is reflected in various genes associated with gastric cancer development, with a focus on cag pathogenicity island (cagPAI), the vacuolating cytotoxin A (VacA), urease, flagella, the hopQ adhesin gene, sialic acid-binding adhesin (SabA), outer inflammatory protein (OipA), the blood group antigen-binding adhesin (BabA) gene and so on (Table 2) [39, 40].

CagPAI and cytotoxin-associated gene A (CagA)

CagPAI is a widely distributed genetic marker found in *H. pylori* strains, believed to have been acquired by an ancestral strain prior to the migration of the modern humans out of Africa [22, 41]. This 40 kb gene cluster, comprising 31 open reading frames, encodes the type IV secretion system (T4SS) and the effector proteins such as CagA, which plays a key role in gastric carcinogenesis (Fig. 1A) [42].

CagA, a 120 to 140 kD protein with distinct amino-terminal domains [23], is translocated into gastric epithelial cells via the T4SS [43]. Once internalized into the epithelial cells, it is phosphorylated by the host c-SRC and c-ABL tyrosine kinases at the glutamate-proline-isoleucine-tyrosine-alanine (EPIYA) motifs [24, 44], enabling it to interact with SHP2 and trigger the downstream signaling cascades [45]. CagA has multiple influences on host epithelial cells. These effects broadly lead to cytoskeletal rearrangements, inhibition of epithelial cell apoptosis, disruption of intercellular junctions, and phenotypes associated with epithelial-mesenchymal transition (EMT) and uncontrolled cell proliferation. Additionally, CagA also induces inflammatory signaling pathways that results in recruitment of inflammatory cells and altered immune microenvironment, leading to the recognition of CagA served as a oncoprotein of *H. pylori* [46].

The virulence of CagA relies on the type and number of EPIYA sequences it contains [25]. There are currently four types of cagA EPIYA sequences (A, B, C, D), and EPIYA-A and EPIYA-B were found in almost all *H. pylori* cagA (Fig. 1B). *H. pylori* strains in Western countries often carry the EPIYA-C sequence, while East Asian strains frequently possess the EPIYA-D sequence [39, 47, 48]. Strains containing EPIYA-D are reported to be linked to a higher risk of gastric cancer due to the enhanced binding affinity with SHP2 [49, 50]. CagA could interact with host SHIP2, an SH2 domain-containing phosphatidylinositol 5'-phosphatase, which facilitates its subsequent delivery into gastric epithelial cells [51]. *H. pylori* East Asian-type CagA demonstrated more powerful dysregulation on intracellular signalings, especially more severe intracellular hypoxia and higher levels of reactive oxygen species (ROS) [52]. Furthermore, a recent research has shown that *H. pylori* strains with additional EPIYA-C sequences may induce the transcription of host genes participated in gastric cancer progression, including erbB2, HGF-R, FGFR4, and TGF-β [53].

Vacuolating cytotoxin A (VacA)

VacA, a key secreted cytotoxin generated by *H. pylori*, is a pore-forming toxin that plays a key functional role in inducing vacuolation of host cells. The N-terminal p33 subunit of VacA forms anion channels, while the p55 subunit acts on epithelial cells to induce cell apoptosis [54, 55]. VacA also inhibits T cell development and proliferation, impairs mitochondrial function and autophagy, and damages cell polarity [44, 56]. Additionally, VacA is involved in the excessive release of IL-8 and alterations in cellular amino acid homeostasis, leading to autophagy inhibition [27, 28].

In fact, nearly all *H. pylori* strains carry the vacA gene. The vacA gene's vacuolating activity is affected by genetic polymorphisms in four identified variable regions: signal (s) region (s1 and s2), the intermediate (i) region (i1, i2, and i3), the middle (m) region (m1 and m2), and the

Table 2 The mechanism and function of *H. Pylori* virulence factor

H. pylori virulence factor	Mechanism and function	References
CagPAI and CagA	CagPAI encodes the type IV secretion system (T4SS) and effector protein CagA. CagA is translocated into epithelial cells, where it phosphorylates and triggers signaling cascades associated with gastric cancer pathogenesis.	[22, 23, 24, 25, 26]
VacA	VacA is a secreted toxin that induces vacuolation in host cells. It affects T cell proliferation, mitochondrial function, apoptosis, IL-8 release, and autophagy. Genetic polymorphisms in VacA influence its activity and are associated with the risk of gastric cancer.	[27, 28, 29, 30, 31]
Urease	Urease hydrolyzes urea to neutralize stomach acid and maintain an optimal pH for bacterial survival.	[32, 33, 34]
Flagella	Flagella facilitate bacterial movement and colonization. They also contribute to biofilm formation and modulate the immune response by inducing the release of IL-8.	[33, 35, 36]
Outer membrane proteins (OMPs)	OMPs like BabA, SabA, and OipA interact with host receptors, promoting long-term colonization, chronic inflammation, and IL-8 secretion.	[21, 36–38]

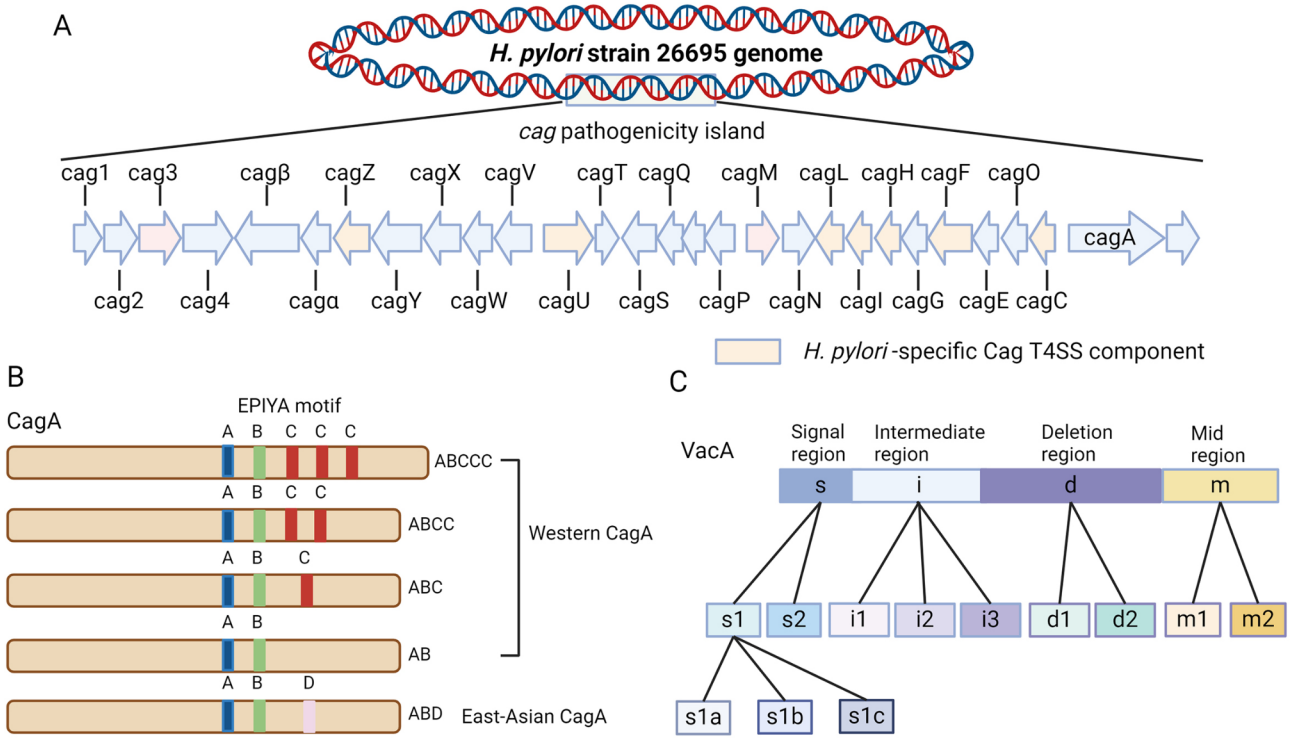

Fig. 1 Organization of genes within the cagPAI and CagA/VacA variations. (**A**) Arrangement of cagPAI genes in *H. pylori* strain 26,695. The cagPAI genes and gene order are relatively well-conserved. Cag3, cagY, cagX, cagT, and cagM encoding proteins localized to the T4SS. *H. pylori*-specific Cag T4SS components are indicated. (**B**) Western *H. pylori* strains possess a form of CagA that contains the EPIYA-A and EPIYA-B regions, followed by 1–3 repeats of EPIYA-C region. East-Asian strains of *H. pylori* possess a form of CagA that contains EPIYA-D region instead of EPIYA-C region. (**C**) There are three main regions of diversity within the VacA passenger domain, designated the s, i, and m regions; within each region, sequences can be classified into: s1 or s2, i1, i2 or i3, d1 or d2, and m1 or m2. s1 can be classified into three main types (s1a, s1b, or s1c). Multiple possible combinations can be present in different *H. pylori* strains as a result of recombination. Figure generated from studies described in references 22, 25, and 33

deletion (d) region (d1 and d2) (Fig. 1C) [29, 57]. The vacA i region is a key contributor of VacA toxin activity, with i1 being the most powerful [30, 58]. The vacA s1/m1 alleles exhibit the most cytotoxic activity, followed by s1/m2 genotypes, while the s2/m2 genotypes show the lowest cytotoxic activity [31, 58, 59]. Studies have shown that specific vacA genotypes are correlated with an increased risk of gastric cancer development [60, 61]. In addition, different genotypes are related with specific gastric cancer types [58]. For example, vacA i1 is associated with intestinal-type adenocarcinoma, while vacA d1 is correlated with diffuse-type adenocarcinoma [62]. Additionally, interactions between VacA and CagA have been shown to promote the effective colonization in the iron-limited conditions of the stomach and participate in gastric cancer development through autophagy regulation [63, 64]. Recent studies suggest that VacA may indirectly influence the STAT3 signaling pathway by modulating the inflammatory and immune responses in gastric microenvironment. VacA could also reduce the STAT3, Bcl-2, and Bcl-XL expressions in a dose-dependent manner [65].

Other virulence factors

Beyond CagA and VacA, *H. pylori* evolved a series of virulence factors to ensure its survival and pathogenicity [37]. The stomach presents a harsh environment for bacterial colonization. Urease and flagella are crucial for survival in the acidic gastric environment with a pH of 1–2 [35]. Urease generates ammonia and carbon dioxide by hydrolyzing urea, neutralizing stomach acid and maintaining an optimal pH for survival [32, 66]. Additionally, *H. pylori* pathogenicity is not limited to neutralizing gastric acid with urease. Flagellar-based motility facilitates bacterial colonization, promoting the penetration of gastric mucus [33, 36]. In addition, urease activity is also involved in the flagellar motility and immunological response modulation by inducing the release of IL-8, which recruits immune cells and promotes inflammation, contributing to the persistent infection and mucosal damage [27, 34].

Outer membrane proteins (OMPs), including BabA, SabA, and OipA, interact with receptors on human epithelial cells, facilitating the binding to host cells and chronic inflammation through IL-8 secretion [38, 67]. This intricate suite of virulence factors underscores *H.*

pylori's ability to persist within the host and contribute to gastric cancer.

Molecular mechanisms of *H. Pylori* in gastric carcinogenesis

The complex biological processes and molecular mechanisms behind gastric cancer pathogenesis remain unclear. Dysregulation of numerous pathways plays an important role during gastric carcinogenesis. The development of gastric cancer involves the following mechanisms that can activate the downstream signaling pathways (Table 3), including the cytokine-stimulated transduction (JAK-STAT) signaling, the nuclear factor κB (NF-κB) pathway, the Wnt/β-catenin signaling pathway, the mitogen-activated protein kinase (MAPK) pathway, the Hippo pathway, the PI3K/Akt pathway, and other signaling pathways [92]. The molecular interplay between *H. pylori* and the host involves a sophisticated regulation of molecular mechanisms that contribute to gastric carcinogenesis (Fig. 2). This section delves into the key molecular mechanisms through which *H. pylori* manipulates the host cellular processes to promote gastric carcinogenesis.

STAT3 signaling

The transcription factor STAT3 is instrumental in the gastric cancer progression stimulated by *H. pylori*. Once cytokines such as IL-6, IL-11, TNF, and IL-17 bind to their specific cellular receptors, they trigger the phosphorylation of receptor-associated tyrosine kinases, including JAK1, JAK2, Src, and EGFRs [68, 93]. Subsequently, STAT3 undergoes phosphorylation (p-STAT3), which is in turn translocated to the nucleus, where it modulates the transcription of downstream target genes that participate in numerous cellular processes, such as inflamation, proliferation, EMT, invasion, and metastasis (Fig. 3) [69, 70].

H. pylori can activate the STAT3 pathway through multiple molecular mechanisms. It is capable of continuously activating STAT3 by upregulating IL-6 [71]. In addition, *H. pylori*'s virulence factor CagA delivered into the host epithelial cells, triggered sustained STAT3 activation through the SHP-2 pathway, and stimulated the transcription of downstream STAT3 target genes [72]. Further, *H. pylori* interacted with Toll-like receptor 2 (TLR2), amplifying inflammatory responses and reinforcing STAT3 activation [94, 95]. Our recent work has also demonstrated that STAT3-induced overexpression of DAB2 through SRC-YAP1 pathway to enhance the *H. pylori*-stimulated gastric carcinogenesis [96]. Moreover, it is interesting to note that FGFR4 induction by *H. pylori* infection via STAT3 signaling has been participated in the biology of gastric cancer [97]. Under certain conditions, *H. pylori* has also been reported to downregulate other components of the JAK-STAT pathway, potentially as a strategy for immune evasion [98, 99].

In conclusion, sustained activation of STAT3 represents a key molecular mechanism by which *H. pylori* promotes gastric carcinogenesis. This pathway, regulated by virulence factors such as CagA and other signalings like TLRs, triggers complicated oncogenic effects, including but not limited to cell proliferation, differentiation, inhibition of apoptosis, and EMT. Elucidating the comprehensive mechanisms of STAT3 activation will provide novel strategies for the prevention and treatment of gastric cancer.

NF-κB pathway

NF-κB is a key nuclear transcription factor in gastric carcinogenesis initiated by *H. pylori* (Fig. 4). The NF-κB pathway is not only involved in the regulation of inflammatory responses, but also directly mediates the promotion of tumorigenesis [73].

H. pylori activates NF-κB through multiple pathways. CagA can directly activate NF-κB and promote its translocation into nucleus [100]. Furthermore, *H. pylori* activates the upstream IKK kinase complex, initiating the

Table 3 Signaling pathways activated by *H. Pylori*

Signaling pathways	Molecular mechanisms involved in gastric cancer induced by H. pylori	References
STAT3 signaling	*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.	[68–72]
NF-κB pathway	*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.	[73, 74, 75–77, 78]
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.	[79–81, 82, 83]
Other signaling pathways	*H. pylori* activates additional signaling pathways including the MAPK pathway (ERK, JNK, p38), PI3K/Akt pathway, Hippo pathway, and various other pathways (HGF/Met, TGF-β, Hedgehog, 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.	[84–91]

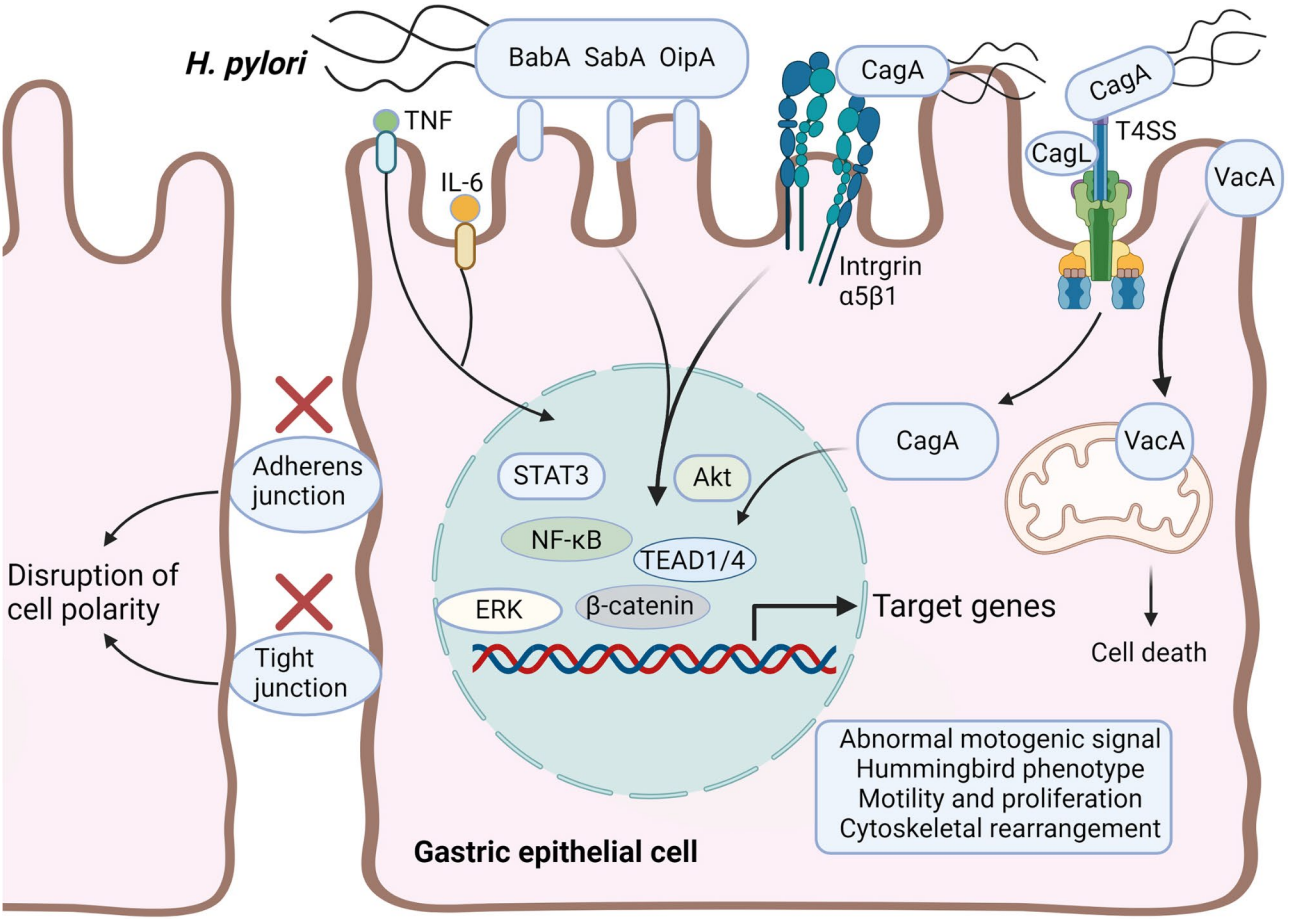

Fig. 2 The development of gastric cancer is induced by *H. pylori*. Key aspects of bacterial pathopoiesis involve flagellar motility, mechanisms of adhesion, disruption of intercellular junctions, and damage to the gastric epithelium via vacuolization. The *H. pylori* virulence factors activate STAT3, NF-κB, ERK, Akt, and Wnt/β-catenin signaling pathways, and exert key roles in abnormal motogenic signal, hummingbird phenotype, motility and proliferation, cytoskeletal rearrangement, and disruption of cell polarity, leading to gastric carcinogenesis

NF-κB pathway by upregulating the expression of pro-inflammatory factors including TNF-α and IL-1β [74, 101]. Additionally, NF-κB activates the expression of the inflammatory cytokine IL-32, which further promotes the expression of NF-κB to form a forward loop [102]. Notably, NF-κB-dependent overexpression of hepatocyte nuclear factor 4α (HNF4α), peroxiredoxin 2 (PRDX2), and caudal-type homeobox 2 (CDX2) regulates gastric cancer development after *H. pylori* infection [75]. The latest study has found that *H. pylori* could activate the PIEZO1-YAP1-CTGF axis through NF-κB, reshaping the gastric cancer microenvironment to promote gastric cancer development [76]. *H. pylori* infection can also stimulate RASAL2 expression through NF-κB-dependent pathway, enhancing gastric carcinogenesis via β-catenin signaling [77]. Meanwhile, the activation of NF-κB leads to the transcription of genes that enhance cell cycle progression, inhibit apoptosis, and promote angiogenesis, thereby fostering a tumor-supportive environment [103, 104]. Furthermore, NF-κB cross-regulates with other key tumor signaling pathways, such as STAT3 and HIF-1α, collaboratively promoting gastric tumorigenesis [78].

In conclusion, the NF-κB pathway functions as a key effector in the development of *H. pylori*-mediated gastric cancer. It is not only involved in the manipulation of the immune responses but also directly drives various carcinogenic behaviors of tumor cells. Its upstream and downstream molecular network offers insights into the carcinogenic mechanisms and potential new therapeutic targets.

Wnt/β-catenin

Wnt/β-catenin signaling pathway is a key regulatory mechanism in *H. pylori*-related gastric cancer (Figs. 3 and 4). Extensive evidence indicates that sustained activation of Wnt/β-catenin pathway is closely correlated with the occurrence, progression, and aggressiveness of gastric cancer [79, 80].

Firstly, the Wnt/β-catenin pathway is a pivotal component in the early stage of gastric carcinogenesis induced

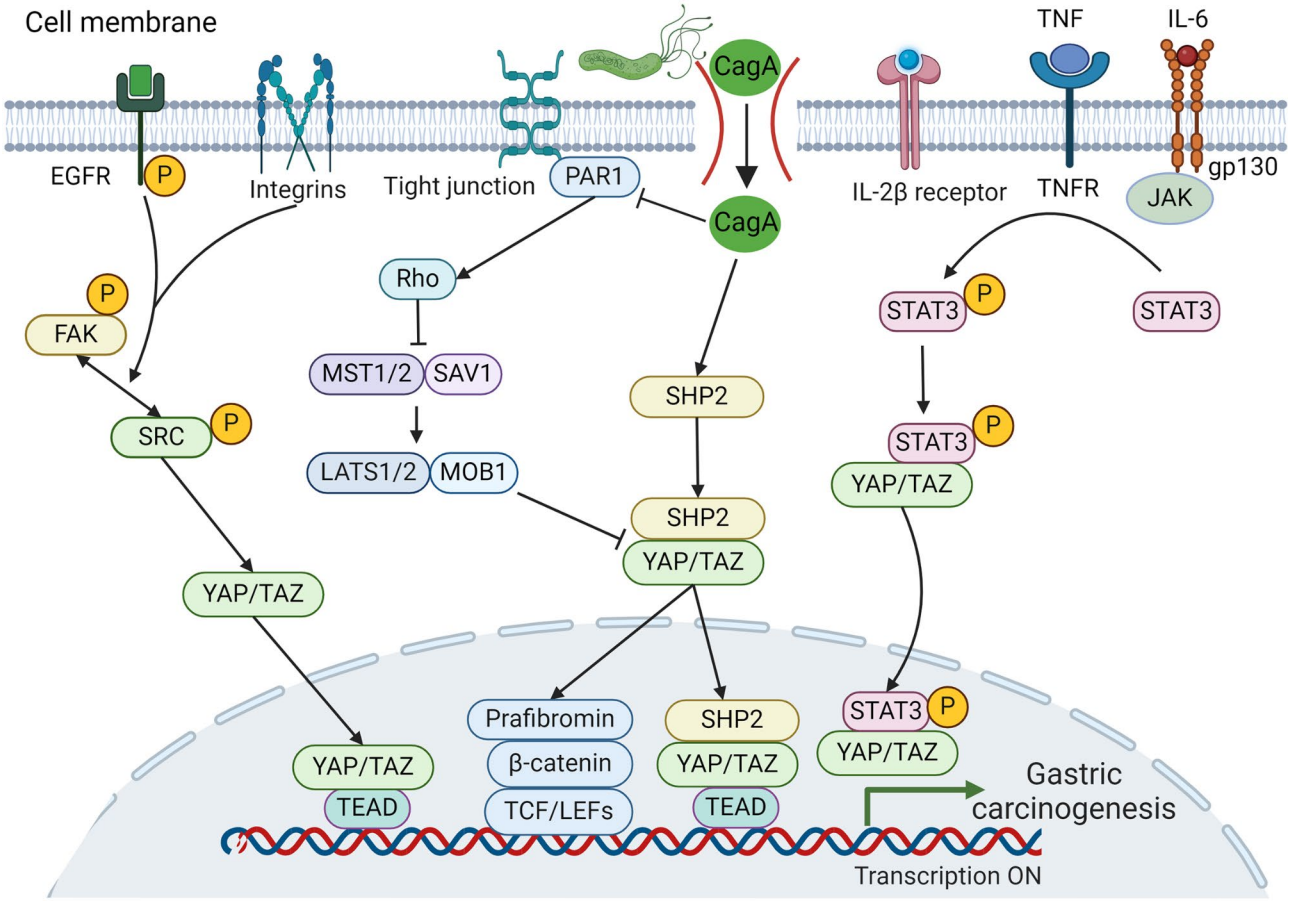

Fig. 3 Aberrant Wnt/β-catenin, STAT3, and Hippo/YAP signaling pathways activation in *H. pylori*-induced gastric cancer. *H. pylori* infection and inflammatory cytokines can activate the Wnt/β-catenin, STAT3, and Hippo/YAP signaling pathways, leading to the onset of gastric tumorigenesis. *H. pylori* infection activates EGFR, leading to FAK/SRC/YAP activation. *H. pylori* infection can also disturb the tight junction and activate SHP2, leading to Wnt/β-catenin and Hippo/YAP signals activitation. Inflammatory cytokines such as IL-6 and TNF could directly activate STAT3/YAP signaling pathway

by *H. pylori*. Interestingly, it has been found that *H. pylori* can disrupt a Wnt-dependent cellular polarity mechanism, which is associated with *H. pylori* infection-induced stem cell proliferation and enteroendocrine differentiation [81]. This pathway is activated by CagA, which facilitates the accumulation and nuclear translocation of β-catenin [105]. CagA interacts with LRP8 to form the CagA/LRP8/β-catenin complex, which further amplifies *H. pylori*-induced β-catenin nuclear translocation to drive gastric carcinogenesis [105]. Once accumulates in the nucleus, β-catenin acts as a transcription factor, activating a suite of genes that can disrupt cell cycle regulation, inhibit apoptosis and promote stem cell renewal and homeostasis, thereby fostering a tumorigenic environment [82, 106]. A key mechanism by which *H. pylori* activates the Wnt/β-catenin signaling pathway involves the promotion of ASCL1-mediated aquaporin-5 (AQP5) expression, which contributes to inflammation and gastritis [107]. This activation not only initiates the inflammatory response but also sets the stage for further dysregulation of cellular processes. Moreover, the Wnt/β-catenin pathway is intricately linked to EMT, a process that epithelial cells undergo phenotypic alterations, acquiring a mesenchymal phenotype that is crucial for tumor progression [108]. Nuclear translocation of β-catenin induces the expression of EMT transcription factors, driving the transition and endowing tumor cells with stem cell-like capabilities [109]. The activation of Wnt/β-catenin pathway also directly stimulates tumor cell proliferation, motility, and invasion—hallmarks of gastric carcinogenesis [110]. β-catenin could interact with TCF/LEF transcription factors to upregulate the expression of oncogenes such as MYC, CCND1, and LGR5 [111], which are key drivers of cell cycle progression and tumor proliferation. Furthermore, the Wnt/β-catenin pathway is part of a complex network of cross-regulatory interactions with other tumor signaling pathways influenced by *H. pylori*, leading to a synergistic enhancement of oncogenic effects. A study recently carried out by Sharafutdinov et al. demonstrated that *H. pylori* infection activated NF-κB-induced inflammation and cell proliferation via regulating the Wnt/β-catenin

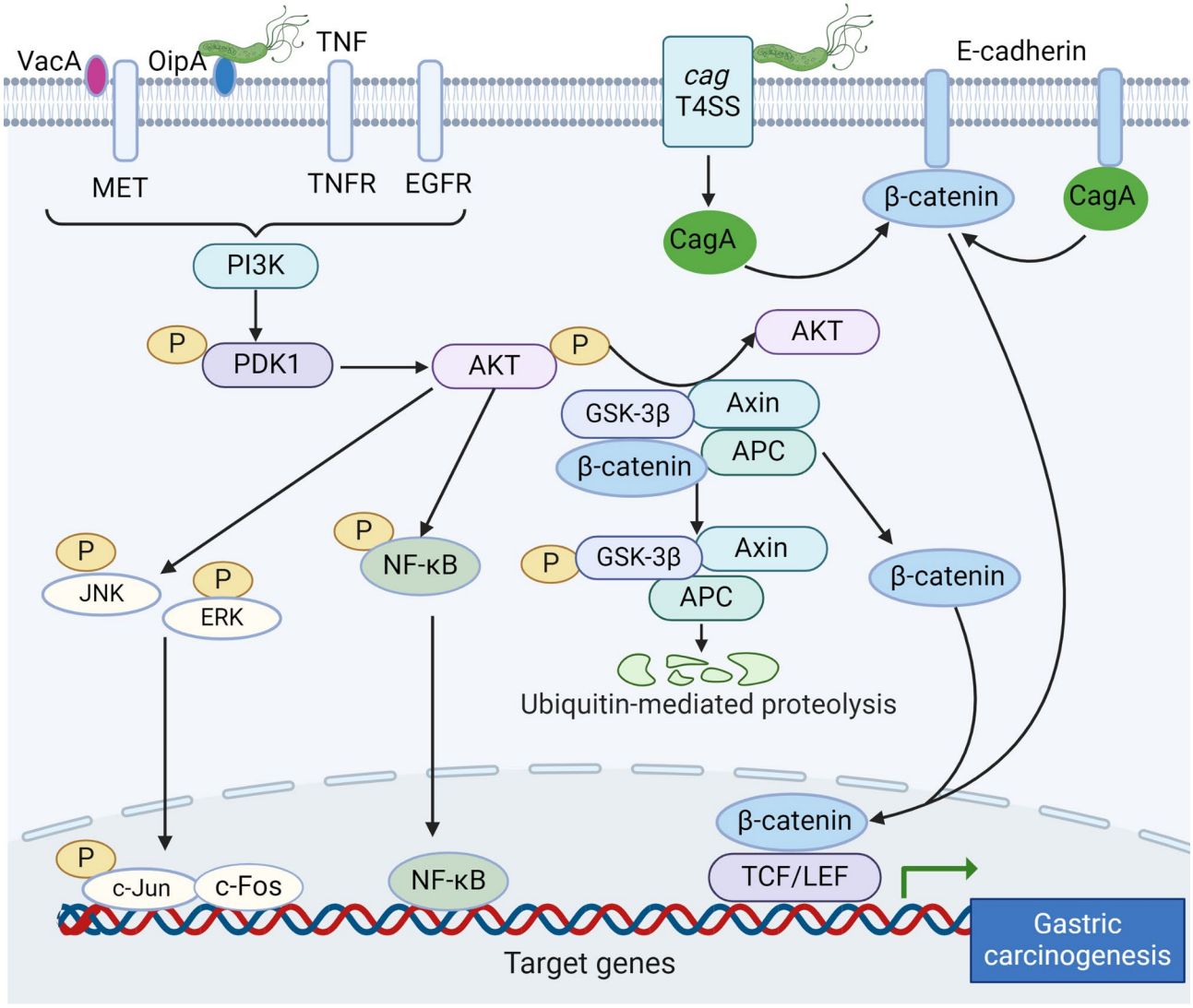

Fig. 4 Signaling pathways regulated by *H. pylori*. Following *H. pylori* adherence, signallings by the CagA, VacA, OpiA and TNF lead to the activation of Akt, further leading to the activation of JNK/ERK, Wnt/β-catenin and NF-κB. Meanwhile, CagA can also directly activate Wnt/β-catenin pathway

pathway, thus triggering malignant transformation [83]. *H. pylori* infection could also significantly enhance YAP and β-catenin nuclear accumulation, and transcriptional activity via their physical interaction to enhance *H. pylori*-induced gastric carcinogenesis [112].

In conclusion, Wnt/β-catenin signaling pathway is an important driving factor for the induction of gastric cancer by *H. pylori*, and this pathway plays a crucial role in various stages of carcinogenesis, including the early initiation and progression of gastric cancer. Understanding these interconnected pathways is essential for revealing the comprehensive molecular landscape of *H. pylori*-induced gastric carcinogenesis.

Other signaling pathways

In addition to the key pathways such as STAT3, NF-κB, and Wnt/β-catenin, *H. pylori* is also capable of activating additional cancer-related signals, which are intricately associated with tumor growth, cell survival, and metastasis, participating in the development of gastric cancer (Figs. 3 and 4).

The mitogen-activated protein kinase (MAPK) pathway: The three main MAPK pathways (ERK, JNK and p38) are all affected by *H. pylori* infection and play an important role in gastric cancer. *H. pylori* is capable of continuously activating the ERK pathway, enhancing cell proliferation and survival [84, 85]. The *H. pylori* T4SS is involved in the regulation of cellular stress response and inflammation through CagA and JNK-dependent pathways [85]. CagA promotes cell ferroptosis susceptibility by ether lipid biosynthesis, which is mediated by the activation of the MEK/ERK/SRF axis [113]. In particular, these MAPK pathways also have complex interactive

regulation with NF-κB and STAT3, so that ERK can activate NF-κB, while JNK can enhance STAT3 activity [86].

The Hippo pathway: Hippo pathway dysregulation is very common in gastric carcinogenesis. Hippo pathway contains a series of phosphorylation cascades in which the mammalian sterile 20-like kinase 1 and 2 (MST1/2) bind the salvador homolog 1 (SAV1) and subsequently activate the large tumor suppressor 1 and 2 (LATS1/2) by phosphorylation, collectively with MOB kinase activator 1 A and 1B (MOB1A/B) to phosphorylate YAP/TAZ, thus restricting the activities of transcriptional coactivators YAP and TAZ [87]. On the contrary, when YAP/TAZ are active, they translocate into the nucleus and interact with the TEAD transcription factor family to promote the expression of downstream genes [114]. Activation of the YAP signal may be one of *H. pylori*'s primary molecular mechanisms linking chronic gastritis to gastric carcinogenesis, with inducing inflammatory responses and immune cell recruitment, which subsequently promotes the generation of IL-6, IL-1, and contributes to tumor formation [115]. CagA promotes the tight junctions degradation via partitioning-defective 1 (PAR1) deregulation [88], a serine/threonine kinase participated in modulation of cellular polarity, subsequently induces YAP/TAZ-mediated gene transcription. Moreover, CagA binds to cytoplasmic SH2-domain-containing protein tyrosine phosphatase-2 (SHP2), resulting in the activation of SHP2 phosphatase [89]. SHP2 is necessary for the activation of the RAS-ERK pathway, and YAP/TAZ could physically bind to SHP2 to enhance its nuclear translocation [116]. Nuclear SHP2 also promotes the parafibromin/β-catenin complex to enhance the β-catenin transcriptional activity, subsequently upregulating Wnt downstream genes [117]. Thus, CagA-mediated SHP2 activation induces the interaction between the Hippo and Wnt/β-catenin pathways.

The PI3K/Akt pathway: *H. pylori* virulence molecules are able to activate the PI3K/Akt pathway, which is closely correlated to the proliferation, survival, migration, and invasion of gastric cancer [86]. Activation of the PI3K/Akt pathway not only upregulates cyclins such as CCND1, but also suppresses apoptotic progression [118]. Furthermore, Akt induces the EMT process in gastric cancer by promoting the activation of EMT transcription factors such as Snail and Twist [119]. CagA enhanced HDM2 protein phosphorylation to induce CK2β degradation, further triggering the activation of Akt to promote EMT in gastric cancer [120]. The PI3K/Akt pathway is mutually regulated with upstream growth factor receptors such as EGFR and HER2, as well as downstream targets such as mTOR and NF-κB [121]. Infection of gastric epithelial cells with *H. pylori* activates PI3K/Akt/mTOR cascades, inducing the transformation of gastric epithelial cells into neoplastic cells [122]. Additionally, *H. pylori* CagA endows gastric cancer stem cell-like characteristics by the activation of the PI3K/Akt/FOXO3a pathway [123].

Other pathways: *H. pylori* can activate HGF/Met, TGF-β, Hedgehog, Notch, and many other signaling pathways that are closely related to tumor development [90, 124–126]. These pathways regulate the proliferation, differentiation, apoptosis, and stem cell properties of gastric epithelial cells. Notably, intricate cross-regulatory networks were continuously activated, including the interaction between Wnt/β-catenin and Notch/Hedgehog pathways, leading to the synergistic enhancement of multiple oncogenic effects [91].

Cellular mechanisms of *H. Pylori* in gastric carcinogenesis

Oxidative stress

Accumulating evidence has revealed that oxidative stress, which is characterized by an elevated level of ROS and reactive nitrogen species (RNS), is involved in the development of gastric cancer. It has been demonstrated that oxidative stress is a critical mechanism through which *H. pylori* induces gastric carcinogenesis [127–129]. This process disrupts the antioxidant defense system and metabolic balance of gastric epithelial cells, thus promoting the carcinogenesis.

Mechanisms of *H. Pylori*-induced oxidative stress

H. pylori induces oxidative stress via the over-production of ROS and RNS [130]. This occurs via both direct and indirect mechanisms [131]. Directly, the bacterium's metabolism generates superoxide and hydrogen peroxide, while virulence factors like CagA and VacA contribute to ROS formation within gastric cells. Indirectly, *H. pylori* triggers a sustained inflammatory response, resulting in the infiltration of neutrophils and macrophages that produce ROS/RNS [132, 133]. A recent work has demonstrated that cells with deficient DNA repair mechanisms lead to more serious oxidative stress and DNA damage during *H. pylori* infection [134, 135]. Additionally, *H. pylori* upregulates the expression of enzymes such as NADPH oxidase and iNOS, exacerbating oxidative stress [136]. Another mechanism of *H. pylori*-stimulated oxidative stress within the gastric epithelial cells is the spermine oxidase, which is an enzyme to catabolize the polyamine spermine and produce H_2O_2 [137].

DNA damage and genomic instability due to oxidative stress

Oxidative stress caused by *H. pylori* results in elevated levels of ROS and RNS, which further lead to various types of DNA damage, such as double-strand breaks and base oxidation. If left unrepaired, these damages can escalate into genetic mutations and chromosomal

rearrangements, thereby accelerating genomic instability [138, 139]. *H. pylori* infection is often linked to enhanced DNA oxidation, damage, and microsatellite instability [133]. The ability of *H. pylori* to cause DNA strand breaks likely results in genomic instability, which in turn contributes to cellular transformation and facilitates the gastric carcinogenesis [140, 141]. Furthermore, the bacterium can impair the function of DNA repair mechanisms, such as by inhibiting the expression of DNA repair genes like OGG1 [142]. In addition, *H. pylori*-colonized host gastric epithelial cells with defects of DNA repair are more inclined to oxidative stress and DNA damage, which significantly intensify the risk of gastric cancer [143, 144].

Disruption of antioxidant defenses and cellular metabolic disorders

The human's antioxidant defense system is designed to counteract oxidative stress. However, *H. pylori* can disrupt this system by dysregulating the expression and activity of antioxidants including superoxide dismutase (SOD), thioredoxin (Trx), apurinic/apyrimidinic endonuclease 1 (APE1), and glutathione (GSH) [132, 145]. Moreover, the bacterium can deplete antioxidants such as vitamins C and E from the gastric mucosa [146], weakening the host's antioxidant defenses. It has been also reported that PRDX-2 could effectively eliminate the oxidant of ROS and H_2O_2 to protect gastric mucosa against atypical proliferation induced by *H. pylori* infection [147].

Oxidative stress can also result in cellular metabolic disorders, potentially blocking the pyruvate and tricarboxylic acid cycles and enhancing glycolysis, which in turn raise the intracellular ROS levels. Mitochondrial dysfunction further amplifies oxidative stress, creating a self-perpetuating cycle of damage [148]. Neutrophils play a significant role in this process, as they can induce the generation of ROS and RNS by upregulating the expression of NOX and iNOS [149, 150].

In summary, *H. pylori*-induced oxidative stress sets the stage for the initiation and progression of gastric cancer through multiple mechanisms including DNA damage, genomic instability, the undermining of antioxidant defenses, and metabolic disruptions. Strategies aimed at inhibiting the oxidative stress or the elevation of antioxidant defenses may provide novel approaches to combat gastric cancer.

DNA damage

Types of DNA damage caused by H. Pylori

H. pylori infection causes various types of DNA damage, which is one of the important mechanisms by which this bacterium promotes gastric carcinogenesis (Table 4). The major forms of DNA damage include: (1) Oxidative DNA damage: *H. pylori*-induced oxidative stress leads to the formation of oxidized DNA base adducts, such as 8-hydroxy-2'-deoxyguanosine (8-OHdG), and sugar oxidation products. These alterations can lead to mutations and genomic instability [151]. (2) Double-strand breaks (DSBs): *H. pylori* releases secreted proteins and virulence factors that can induce DNA double-strand breaks. These breaks, if not properly repaired, can result in chromosomal rearrangements and contribute to gastric carcinogenesis [152]. (3) Ribosomal restriction and digestion damage: *H. pylori* activates ribosomal enzymes that can cleave RNA and cause DNA damage, adding to genomic instability [153]. (4) Microsatellite instability (MSI): Virulent strains of *H. pylori* are often associated with MSI, particularly the high-frequency type (MSI-H) [154, 155]. This association leads to an increased rate of mutations in microsatellite sequences within gastric mucosal tissue [156].

Role of genomic instability in gastric carcinogenesis

Genomic instability, marked by gene mutations and chromosomal aberrations, is a key driver in cancer development. *H. pylori* infection has been linked to a high frequency of gene copy number variations, chromosomal

Table 4 *H. Pylori*-induced DNA damage types and research gaps

Type of DNA damage	Mechanism and effect	Key studies	Research gaps
Oxidative DNA Damage	*H. pylori*-induced oxidative stress leads to formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG) and other oxidized DNA base adducts, contributing to the mutations and genomic instability.	[149]	Limited understanding of specific oxidative damage pathways and their direct link to tumorigenesis.
Double-Strand Breaks (DSBs)	*H. pylori* secretes virulence factors causing various DSBs. Improper repair of these breaks may result in chromosomal rearrangements.	[150]	The exact mechanisms through which *H. pylori* virulence factors induce DSBs remain unclear.
Ribosomal Restriction and Digestion Damage	*H. pylori* activates ribosomal enzymes that can cleave RNA, adding to genomic instability.	[151]	Few studies on the long-term effects of ribosomal damage on DNA stability and its role in gastric cancer.
Microsatellite Instability (MSI)	Virulent strains of *H. pylori* are linked to high-frequency MSI, increasing mutation rates in microsatellite sequences	[152, 153]	Limited data on the clinical implications of MSI induced by *H. pylori* in different gastric cancer patient populations.

duplications, and deletions in gastric cancer tissues [157]. These genomic changes can disrupt the normal function of tumor suppressors and oncogenes, thereby promoting cellular transformation.

Different strains of *H. pylori* can induce various levels of genomic instability, with CagA-positive strains causing more severe MSI and chromosomal deletions [158]. In addition, *H. pylori* infection inhibits the function of p53 tumor suppressor, thus promoting the proliferation of CagA-delivered cells and enhancing the genomic instability [159].

Changes in DNA damage response pathways and DNA repair mechanisms

The complex DNA damage response and repair mechanisms are often compromised by *H. pylori* infection. *H. pylori* downregulates the expression of key DNA damage response genes, such as ATM, p53, and p21, reducing the cell's ability to detect and repair DNA damage [160].

Furthermore, *H. pylori* can impair DNA repair pathways, such as the nucleotide excision repair (NER) pathway [161], and disrupt the machinery for repairing DNA DSBs, impairing both homologous recombination and non-homologous end-joining activities [78]. The chronic inflammatory state induced by *H. pylori* leads to immune cell infiltration and the release of ROS/RNS, causing further DNA damage and sustained cell proliferation [162]. The dysfunction of the DNA damage responses and repair systems due to *H. pylori* infection exacerbates DNA damage and gene mutations, facilitating the progression from chronic gastritis to gastric cancer.

In summary, *H. pylori* induces multiple DNA lesions, triggers genomic instability, and interferes with DNA repair mechanisms, creating an environment conducive to gastric cancer. Understanding these molecular mechanisms is crucial for identifying novel preventive and therapeutic targets.

Inflammatory response

The chronic inflammatory response triggered by *H. pylori* is a significant risk factor for gastric carcinogenesis, involving complex interactions with other carcinogenic processes, such as oxidative stress and aberrant activation of cancer pathways [163, 164].

H. Pylori-induced chronic inflammatory response and its mechanism

H. pylori infection continuously activates both innate and adaptive immune responses, leading to the accumulation of various immune cells in gastric mucosa [165, 166]. These cells release cytokines, chemical mediators, and ROS, which cumulatively damage gastric epithelial cells and contribute to a chronic inflammatory environment that facilitates carcinogenesis.

The bacterium initiates the inflammatory response through multiple molecular mechanisms. Upon binding to gastric epithelial cells, *H. pylori* secretes CagA, which altered bile acid metabolism to promote *H. pylori*-induced inflammation and drive gastric carcinogenesis [167]. Additionally, *H. pylori* activates pattern recognition receptors like NOD1/NOD2 [168], further stimulating inflammatory signaling pathways such as MAPK and NF-κB [149]. These signaling cascades lead to the overexpression of inflammatory cytokines (e.g., IL-8, IL-6), chemokines, adhesion molecules, and enzymes like COX-2, perpetuating the recruitment and activation of inflammatory cells like neutrophils and macrophages, thus creating a self-sustaining loop of inflammation.

Roles of specific immune cells in the inflammatory response

1. Neutrophils: As one of the first responders, neutrophils are recruited by chemokines and produce significant amounts of ROS, which induce oxidative stress and contribute to DNA damage in gastric epithelial cells. *H. pylori* exploits neutrophil plasticity as part of its virulence strategy to elicit N1-like subtype differentiation, which is further involved in gastric carcinogenesis [169].
2. Macrophages: Tumor-associated macrophages (TAMs) play a dual role in inflammation and cancer. *H. pylori* infection up-regulated the expression of indoleamine 2,3-dioxygenase (IDO) in macrophages to induce M2 polarization [170]. Moreover, *H. pylori*'s phospholipase A could modulate p38 signaling pathways to regulate macrophage autophagy, promoting *H. pylori*'s evasion of the immune system and enhancing *H. pylori* survival [171].
3. Dendritic Cells: *H. pylori* infection disrupts dendritic cell function, impairing the antigen-presenting capacity of these cells and modulating the adaptive immune response. This may result in immune evasion by *H. pylori* and a prolonged inflammatory response that contributes to carcinogenesis [172].
4. T Lymphocytes: Both CD4 + and CD8 + T cells are recruited in response to *H. pylori* infection. Th1 and Th17 CD4 + T cell subsets promote inflammation by producing cytokines such as IFN-γ and IL-17, which enhance macrophage and neutrophil activity. Chronic activation of T cells, however, may lead to tissue damage and tumor promotion [173].

Role of inflammatory mediators in promoting oncogenesis

A sustained inflammatory state creates a tumor-promoting microenvironment. Inflammatory mediators play a role at various key steps of gastric carcinogenesis. For

instance, cytokines such as IL-6 and TNF-α can activate oncogenic signaling pathways such as STAT3 and NF-κB, inducing oncogene activation [174]. The inflammatory cells recruited by chemokines generate substantial amounts of ROS and RNS, which contribute to DNA damage and genomic instability [175]. Additionally, matrix metalloproteinases secreted by TAMs contribute to tumor cell invasion [176].

Interactions between inflammation and other carcinogenic pathways

The inflammatory response is not an isolated event but interacts with other *H. pylori*-induced carcinogenic pathways in a mutually reinforcing manner. Inflammatory cells, due to their long-term presence, continuously produce ROS/RNS to exacerbate oxidative stress. This oxidative stress, in turn, upregulates the expression of inflammatory factors like IL-8 [177]. The inflammatory response may drive *H. pylori*-induced DNA damage and gene mutations, while DNA damage can amplify the inflammatory response [178]. There are intricate cross-regulatory interactions between inflammatory signals like NF-κB and other oncogenic pathways such as STAT3 and Wnt/β-catenin.

The chronic inflammatory response stimulated by *H. pylori* is a critical mechanism in gastric carcinogenesis. Inflammatory cells and their mediators are involved in multiple stages of gastric carcinogenesis, including DNA damage, gene mutation, and the formation of the tumor microenvironment. The interplay between inflammation and other carcinogenic pathways, including oxidative stress and genomic instability, forms a complex network. Understanding this network is crucial for comprehending *H. pylori* carcinogenesis mechanisms and may reveal novel therapeutic targets.

Cell apoptosis

Deregulation of cell apoptosis is a key event in *H. pylori*-induced gastric carcinogenesis, and *H. pylori* is capable of manipulating apoptosis in gastric epithelial cells to favor tumor survival and expansion. *H. pylori* has also been reported to induce gastric epithelial cell apoptosis in vitro [179, 180].

Effect of *H. Pylori* on apoptosis of gastric epithelial cells

H. pylori exerts a bidirectional effect on apoptosis in gastric epithelial cells, with effects that may vary depending on the stage of infection. In the early stages, *H. pylori* promotes apoptosis as part of the host's defense response. Virulence factors such as VacA can directly activate the mitochondria-mediated intrinsic apoptotic pathway [181], inducing apoptosis through oxidative stress and DNA damage. This apoptotic response is primarily aimed at eliminating infected cells to limit bacterial colonization. However, as the infection progresses, *H. pylori* shifts to inhibit apoptosis, a common phenomenon in gastric cancer tissues and cell lines [109]. This inhibition of apoptosis supports the survival, proliferation, and dissemination of tumor cells [182]. The dual role of *H. pylori* in modulating apoptosis thus depends on the infection stage, with pro-apoptotic effects more prominent during the initial infection and anti-apoptotic mechanisms becoming dominant as the disease progresses toward malignancy.

H. pylori uses various mechanisms to modulate apoptotic pathways. *H. pylori* urease has been reported to bind to the class II MHC molecules on the surfaces of host epithelial cells and induce apoptosis [183]. Additionally, *H. pylori* VacA has been shown to localize specifically to mitochondrial membranes, stimulate cytochrome c release, and activate the mitochondria-dependent apoptotic signalling cascade [184].

Contribution of apoptosis inhibition to tumor development

The inhibition of apoptosis is a critical molecular mechanism in carcinogenesis. *H. pylori*'s chronic infection and the resulting inflammatory state create a conducive environment for tumorigenesis. *H. pylori* induces inflammatory responses and promotes cancer development through the unbalanced immune microenvironment [185]. By inhibiting apoptosis, *H. pylori* enhances the survival of genetically altered cells, initiating the process of tumor formation [186]. *H. pylori* infection leads to a dysregulated immune response characterized by the infiltration of inflammatory cells in the tumor microenvironment, thus secrete numerous inflammatory cytokines, chemokines, and ROS/RNS, resulting in apoptosis, genomic instability, and the development of gastric cancer [187–189].

H. Pylori regulates apoptosis related regulatory pathways

H. pylori regulates the apoptotic level in gastric epithelial cells through multiple regulatory pathways: (1) Bcl-2 family proteins: *H. pylori* upregulates anti-apoptotic molecules including Bcl-2/Bcl-xL while reducing pro-apoptotic molecules like Bax/Bad [190]. (2) PI3K/Akt signaling pathway: Activation of this pathway by *H. pylori* leads to the phosphorylation and regulation of Bcl-2 family members by Akt [191]. (3) NF-κB pathway: *H. pylori* influences gene transcription by upregulating anti-apoptotic genes such as c-IAP2 and survivin via NF-κB pathway [192]. Activation of PPARγ could dampen *H. pylori*-stimulated activation of NF-κB and apoptosis in gastric cells [193]. (4) p53-dependent pathway: *H. pylori* can suppress p53 expression and activity, blocking the p53-mediated apoptotic program [194].

Additionally, *H. pylori*-induced DNA damage and oxidative stress can directly or indirectly regulate the above apoptosis-related pathways [195, 196]. In general, *H. pylori* significantly reduces the apoptosis level of gastric epithelial cells through multiple regulatory effects, creating favorable conditions for tumor initiation and progression. Thus, targeting apoptosis regulation could offer a promising intervention strategy.

Other mechanisms

In addition to oxidative stress, DNA damage, inflammatory response, and apoptosis regulation, *H. pylori* employs additional strategies contributing to gastric cancer development, including interference with cell cycle progression and autophagy [197, 198]. These mechanisms often intersect with known molecular pathways, forming a complex oncogenic network. Emerging research is putting forward new focal points in the field.

Cell cycle regulation and its interplay with other mechanisms

H. pylori infection can disrupt cell cycle checkpoints, resulting in uncontrolled cell cycle progression. Key mechanisms include upregulation of cyclin expression (e.g., cyclin D1, cyclin E) and cyclin-dependent kinases [199], and downregulation of cell cycle inhibitors like p21 and p27 [200]. These effects are primarily mediated through oncogenic pathways such as STAT3, Wnt/β-catenin, and NF-κB. Dysregulation of the cell cycle not only directly promotes cancer cell proliferation but is also closely related to genomic instability and resistance to apoptosis. For instance, failure in cell cycle DNA checkpoint control can impede DNA damage repair, leading to increased accumulation of mutations [201, 202].

The autophagic process and its alterations

Autophagy, a cellular process of self-digestion to regular balance maintenance, plays a dual role in cancer development [203, 204]. Bacteria have developed diverse strategies to escape from autophagy by interfering with host autophagy signaling or the autophagy machinery, and even adopt autophagy for their proliferation [205]. Autophagy manipulation represents a prominent strategy for intracellular *H. pylori* replication and timely release of oncoproteins to induce malignant transformation [68, 206]. When dysregulated, it can contribute to cancer development and progression. *H. pylori* infection significantly alters the autophagy pathway: it induces early autophagy to eliminate cellular damage, but sustained alterations in autophagy affect cell growth, survival, and immune responses [206–208].

Experimental infection study has demonstrated that *H. pylori* infection promotes autophagy in a YAP-dependent manner by promoting beclin 1 and LC3B-II protein expressions and enhancing the autophagosome formation [209]. CAPZA1 served as a negative regulator of autolysosome formation and decreased the risk of gastric carcinogenesis via suppression of the *H. pylori* CagA-degraded autophagy [210]. VacA could target the lysosomal calcium channel TRPML1 to impaire the endolysosomal trafficking and acquire a reservoir for *H. pylori* survival [211]. Recent studies have demonstrated that the autophagy modulation in response to *H. pylori* infection is mostly attributed to VacA, while the *H. pylori* virulence factor gamma-glutamyltranspeptidase (HpGGT) also disturbed the autophagic flux through impairing lysosomal membrane integrity [56, 212, 213].

Other emerging mechanisms

Cutting-edge research is revealing additional mechanisms through which *H. pylori* may induce gastric cancer. These include the mediation of epigenetic changes such as DNA methylation and histone modifications [214, 215], as well as interference with the balance of intestinal microbiota influencing host metabolism and immune status [216, 217]. The roles of immune cells in the tumor microenvironment [218], extracellular vesicles [219], microRNA map [220], and long non-coding RNAs [221] in *H. pylori*-induced carcinogenesis are also emerging as active areas of investigation.

Abnormal DNA methylation, including hypermethylation or deletion of the ARF tumor suppressor gene (p14ARF) and FOXD3, has been associated with *H. pylori*-induced carcinogenesis [222]. DNA methylation of genes (IGF2, SLC16A2, SOX11, P2RX7, and MYOD1) was identified in *H. pylori* infected gastric mucosa, and significantly correlated with specific molecular and clinicopathological features in gastric cancer [223]. *H. pylori* infection leads to hypermethylation of connexins Cx32 and Cx43, inhibiting their expression and the intercellular communication function of the gastric space junction. These effects further contribute to gastric carcinogenesis [224]. Infection with *H. pylori* induced aberrant demethylation of GNB4, which further enhanced gastric carcinogenesis via the Hippo-YAP1 pathway [225].

H. pylori has evolved multifaceted strategies to promote its survival in the face of robust host defense responses. The molecular mechanisms underlying *H. pylori*-promoted carcinogenesis are exceptionally intricate, involving the interplay of numerous pathways and interconnected links. A thorough understanding of this complex network is essential, as it will not only deepen our comprehension of the bacterium's carcinogenic nature but also offer a wealth of potential targets for clinical intervention and disease management (Table 5).

Table 5 Cellular mechanisms involved in gastric cancer induced by *H. Pylori*

Cellular mechanism	Specific mechanism	References
Oxidative stress	*H. pylori* induces oxidative stress through the overproduction of ROS and RNS. This leads to DNA damage, genomic instability, disruption of antioxidant defenses, and metabolic disorders.	[128–130, 132, 136, 142, 145, 147]
DNA damage	*H. pylori* infection causes oxidative DNA damage, DSBs, ribosomal restriction and digestion damage, and MSI. Genomic instability promotes gastric cancer development. *H. pylori* impairs DNA repair mechanisms.	[138, 140, 152, 161]
Inflammatory response	*H. pylori* triggers chronic inflammatory responses, leading to the infiltration of inflammatory cells and the release of cytokines, ROS, and RNS. Inflammatory mediators activate oncogenic signaling pathways, cause DNA damage, and promote tumor cell invasion. The inflammatory responses also interact with oxidative stress and genomic instability.	[163, 164, 168, 175, 176]
Cell apoptosis	*H. pylori* initially induces apoptosis in gastric epithelial cells but later inhibits apoptosis, promoting tumor cell survival, proliferation, and dissemination. This is achieved by the regulation of apoptosis-related regulatory pathways.	[184, 187, 193, 194, 226]
Other mechanisms	*H. pylori* interferes with cell cycle progression and alters the autophagic process. Emerging research focuses on epigenetic changes, intestinal microbiota balance, immune cells in the tumor microenvironment, extracellular vesicles, and long non-coding RNAs in *H. pylori*-induced carcinogenesis.	[202, 204, 205, 208, 210, 212, 220, 221]

H. Pylori infection and its impact on the efficacy of immunotherapies

H. pylori infection can actively manipulate host to establish an immunosuppressive environment that sustains chronic infection [227]. This capability has intriguing implications for the interplay between *H. pylori* and cancer immunotherapies. Observations indicate a negative association between *H. pylori* infection and systemic inflammatory disorders including asthma, inflammatory bowel disease, and eosinophilic esophagitis in human populations [228–231]. This suggests that *H. pylori* may play a key role in mitigating imbalanced systemic immune responses, which could be a double-edged sword in the context of immunotherapy. Moreover, *H. pylori* infection has been found to induce the upregulation of PD-L1 expression in gastric cancer to promote immune evasion [232, 233], indicating the potential influence on the efficacy of immunotherapy for cancers. *H. pylori* upregulates PD-L1 through several signaling pathways, including the NF-κB [234], JAK/STAT [235], and PI3K/Akt pathways [124].

This has sparked increasing interest among scientists to understand the comprehensive impact of *H. pylori* on the efficacy of cancer immunotherapies and its potential role as a prognostic biomarker. Meanwhile, the causality behind the association between PD-L1 expression and *H. pylori* infection should be further explored in the future, and disrupting the potential pathways may offer new therapeutic options for gastric cancer. Recent studies indicate that *H. pylori* infection can detrimentally influence the efficacy of cancer immunotherapies by dampening innate immune responses, such as dendritic cell cross-presentation activities and production of inflammatory cytokines [236, 237]. Consistent with these findings, research led by Magahis et al. has shown that past or current *H. pylori* infection is correlated with a significant decrease in progression-free and overall survival rates in advanced gastric cancer in the treatment of immune checkpoint inhibitors [238]. Compared with the *H. pylori*-negative patients, *H. pylori*-positive patients had a higher nonclinical response to anti-PD-1 therapy in advanced gastric cancer [239]. However, another study suggested that while *H. pylori* infection might create a favorable "hot" tumor microenvironment for gastric cancer immunotherapy, it could adversely impact immunotherapy for other types of cancer such as esophageal squamous cell carcinoma and colorectal adenocarcinoma [154], highlighting the complex and potentially dualistic role of *H. pylori* in cancer treatment.

These findings collectively emphasize the critical importance of considering a patient's *H. pylori* infection status when contemplating immunotherapy. There is an urgent need for future research to elucidate the intricate immunoregulatory mechanisms of *H. pylori*'s interaction with the immune system. Investigating whether eradicating *H. pylori* infection could enhance the efficacy of immunotherapies is a promising avenue that could lead to more personalized and effective treatment strategies for gastric cancer patients.

Single-nucleotide polymorphisms (SNPs)-based stratification of gastric cancer by *H. Pylori* infection

Genome sequencing studies have identified numerous SNPs in *H. pylori* OMP genes (babA, hopS, hopZ as well as cagX and cagY) that promote rapid host adaptation of this bacterium [240]. *H. pylori* genetic adaptation was further investigated in Mongolian gerbil model. SNPs were mainly identified in genes involved in iron acquisition (fur, tonB1, fecA2, fecA3, and frpB3) or encoding OMPs (alpA, oipA, fecA2, fecA3, frpB3 and cagY) in *H. pylori* strains [241]. Another study also showed gene alterations were more frequent in the hop and hof families of OMPs [242]. In addition, cancer-associated SNPs in bacterial pathogens were detected in gastric cancer pathogen *H. pylori* by genome-wide association studies (GWAS) [243, 244]. GWAS studies demonstrated that

specific SNPs are potentially associated with the development of gastric adenocarcinoma [243, 245, 246].

Notably, Fur R88H SNP has been shown to enhance survival rates against iron deficiency, high salt and oxidative stress conditions, facilitating a significantly selective evolution to *H. pylori* [241, 247]. Interestingly, functional analyses were conducted to detect the effect of the identified SNPs in the development of gastric disease. Further, 171 S-to-171 L SNP in high temperature requirement A (HtrA) enhanced the injection of oncoprotein CagA into gastric mucosal cells, and resulted in more severe NF-κB-induced inflammation, enforced β-catenin-mediated cell proliferation, and higher host DNA DSBs, collectively driving gastric malignant transformation [83]. Cancer-associated SNPs in *H. pylori* pathogen are promising indicators for risk assessment in *H. pylori* infection, and thus to pave the way for future prevention and treatment strategies for individual patients.

Perspectives

The extensive review of the mechanisms by which *H. pylori* contributes to gastric cancer underscores the complexity involving the synergy of multiple pathways and multifactorial nature of this bacterium's role in carcinogenesis. MAPK, PI3K/Akt, and other pathways are intertwined with the classical STAT3, NF-κB, and Wnt/β-catenin pathways, exhibiting multilevel cross-regulation between them and forming an intricate network of oncogenic molecules. It is evident that *H. pylori*'s impact is not limited to a single pathway but encompasses a vast network of molecular and cellular interactions that drive the transformation of gastric epithelial cells. A thorough analysis of the interrelationships between these molecular pathways will provide a more comprehensive understanding of the nature of *H. pylori*-induced gastric carcinogenesis, offering new insights and targets for the prevention and treatment of gastric cancer.

Multiple omics studies have demonstrated various molecular landscapes underlying the development of gastric cancer. However, cellular diversity and intercellular interactions driven by *H. pylori* infection in the Correa cascade of multistep gastric carcinogenesis are still poorly understood, presenting a significant challenge for understanding gastric carcinogenesis. Single-cell transcriptomic profiling has shown enhanced cell-cell interaction and activation of TNF, SPP1, and THY1 signaling pathways during *H. pylori* infection [248]. Interestingly, a recent study demonstrated that significantly higher levels of CD11c + myeloid cells and activated CD4 + T cells and B cells were in gastric mucosa of *H. pylori*-infected individuals compared with uninfected individuals [249]. However, the underlying mechanisms through which *H. pylori* infection and associated intercellular communications lead to gastric carcinogenesis remain unclear, further hindering the development of effective measures to prevent gastric carcinogenesis, and further research is still needed in this area.

Although half of the world's population is infected with *H. pylori*, only a subset of individuals will eventually develop gastric malignancies. As our understanding of these mechanisms deepens, the identification of individuals with a higher risk of gastric cancer should be the primary target for developing targeted therapies and preventive strategies. In addition, GWAS have been shown to be instrumental in identifying cancer-associated SNPs in *H. pylori* [246]. It is possible to stratify the risk for gastric cancer by SNPs in *H. pylori*. However, functional analyses for determining the effect of the identified high-risk SNPs in gastric cancer development are particularly worthy of further investigation. This hypothesis, if confirmed, would have important implications for the development of new interventive measures, such as vaccination to prevent *H. pylori* infection and associated gastric cancer. Future research should focus on: (1) Elucidating the precise mechanisms by which *H. pylori*'s virulence factors interact with host cells to induce carcinogenesis. (2) Investigating the profound influence of bacterial genotype on disease progression and response to treatment. (3) Exploring the complex interactions between *H. pylori* and the host immune system, especially in the background of cancer immunotherapies. (4) Developing novel therapeutic targets and immunotherapies based on the molecular pathways dysregulated by *H. pylori*. (5) Establishing new prevention strategies, including more effective eradication therapies and vaccination strategies, to reduce the global burden of *H. pylori*-related gastric cancer.

As research continues to unravel the complexities of *H. pylori*'s interactions with its host, we are optimistic that these insights will give rise to more effective strategies for the prevention and treatment of gastric cancer, ultimately improving gastric cancer patient outcomes worldwide.

Abbreviations

H. pylori	Helicobacter pylori
STAT3	Signal transducer and activator of transcription 3
NF-κB	Nuclear factor kappa-B
IARC	International Agency for Research on Cancer
cagPAI	Cag pathogenicity island
CagA	Cytotoxin-associated gene A
VacA	Vacuolating cytotoxin A
SabA	Sialic acid-binding adhesin
OipA	Outer inflammatory protein A
BabA	Blood group antigen-binding adhesin
T4SS	Type IV secretion system
EPIYA	Glutamate-proline-isoleucine-tyrosine-alanine
EMT	Epithelial-mesenchymal transition
MAPK	Mitogen-activated protein kinase
TLR	Toll-like receptor
FGFR	Fibroblast Growth Factor Receptor
HNF4α	Hepatocyte nuclear factor 4α
PRDX2	Peroxiredoxin 2
CDX2	Caudal-type homeobox 2

AQP5	Aquaporin-5
PAR1	Partitioning-defective 1
MST1/2	Mammalian sterile 20-like kinase 1 and 2
SAV1	Salvador homolog 1
LATS1/2	Large tumor suppressor 1 and 2
MOB1A/B	MOB kinase activator 1 A and 1B
SHP2	SH2-domain-containing protein tyrosine phosphatase-2
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
SOD	Superoxide dismutase
Trx	Thioredoxin
APE1	Apurinic/apyrimidinic endonuclease 1
GSH	Glutathione
8-OHdG	8-hydroxy-2′-deoxyguanosine
DSBs	Double-strand breaks
MSI	Microsatellite instability
NER	Nucleotide excision repair
TAMs	Tumor-associated macrophages
IDO	Indoleamine 2,3-dioxygenase
GGT	Gamma-glutamyltranspeptidase
SNP	Single-nucleotide polymorphism
GWAS	Genome-wide association studies
HtrA	High temperature requirement A
Rho	Ras homolog family

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