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The Regulatory Mechanism and Therapeutic Targets of the HIPPO Pathway in *Helicobacter pylori*-Associated Gastric Cancer

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Abstract

The HIPPO signaling pathway critically regulates cell proliferation, apoptosis, and tissue homeostasis, playing a pivotal role in *Helicobacter pylori* (*H. pylori*)-associated gastric cancer, a major contributor to the global gastric cancer burden. Dysregulation of HIPPO signaling, particularly through YAP/TAZ activation, drives tumorigenesis, invasion, and metastasis in *H. pylori*-infected gastric tissues. This review elucidates the molecular mechanisms by which *H. pylori* virulence factors, such as CagA, disrupt HIPPO pathway components, including MST1/2 and LATS1/2 kinases, and explores epigenetic and pathway crosstalk mechanisms. We also discuss promising therapeutic targets, including YAP/TAZ inhibitors and combination strategies with *H. pylori* eradication therapies. These insights aim to guide the development of targeted interventions for *H. pylori*-related gastric malignancies.

Keywords

Helicobacter pylori, Gastric Cancer, HIPPO Pathway, YAP/TAZ, CagA

1. Introduction

The HIPPO signaling pathway is a conserved molecular cascade that controls organ size and tissue homeostasis by regulating cell proliferation and apoptosis, with YAP (Yes-associated protein) and TAZ (transcriptional coactivator with PDZ-binding motif) as key downstream effectors that, when activated, promote gene expression driving cell growth and survival. Gastric cancer (GC) ranks as the fifth most common malignancy and the third leading cause of cancer mortality globally, with over 1 million annual cases [1]. *H. pylori*, a Class I carcinogen, is the primary risk factor, initiating a cascade from chronic gastritis to adenocarcinoma [2]. The

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HIPPO pathway, conserved across species, is hijacked in *H. pylori*-driven oncogenesis, promoting epithelial-mesenchymal transition (EMT), metaplasia, and tumor progression [3]. *H. pylori* infects over 50% of the global population, with higher prevalence in developing countries. Chronic infection increases GC risk 2 - 6 fold, influenced by host genetics, diet, and bacterial virulence, particularly cagA-positive strains [4]. Persistent inflammation and oxidative stress from *H. pylori* drive genomic instability and oncogenic signaling [5]. Discovered in the 2000s, the HIPPO pathway inhibits YAP/TAZ to maintain tissue homeostasis. Its dysregulation in cancers, including GC, correlates with aggressive phenotypes and poor survival [6]. In *H. pylori* infection, HIPPO inactivation fosters stemness and EMT, making it a critical therapeutic target [7]. This article reviews how *H. pylori* modulates the HIPPO pathway and identifies therapeutic targets to improve clinical outcomes.

2. Core Components and Regulation of the HIPPO Pathway

The HIPPO pathway integrates mechanical and biochemical signals to control cellular fate through a kinase cascade and transcriptional effectors. Upstream regulators, such as Merlin/NF2 and G-protein-coupled receptors, sense cell polarity and cytoskeletal dynamics, often disrupted in GC by inflammatory stress [8]. Core kinases MST1/2 phosphorylate LATS1/2, which then phosphorylates YAP/TAZ at serine residues (e.g., S127 in YAP), promoting 14-3-3 binding and cytoplasmic retention or proteasomal degradation [9]. *H. pylori* CagA inhibits LATS2, allowing unphosphorylated YAP/TAZ to enter the nucleus and bind TEAD1–4, driving expression of oncogenic genes like CTGF, CYR61, and SOX9 [10]. In GC, YAP/TAZ hyperactivation promotes proliferation, survival, and metastasis, with studies showing elevated YAP levels in *H. pylori*-positive tumors correlating with advanced stages [11].

3. Pathogenic Role of *Helicobacter pylori* in Gastric Cancer

H. pylori colonizes the gastric mucosa, evading immune responses and inducing chronic inflammation. Its virulence factors, notably CagA and VacA, disrupt host signaling. CagA, delivered via the type IV secretion system, mimics host proteins to activate pathways like PI3K/AKT, while VacA causes vacuolation and inhibits apoptosis [12] [13]. Chronic infection triggers NF-κB-mediated cytokine release (e.g., IL-1β, TNF-α), creating a protumorigenic microenvironment that suppresses HIPPO kinases and activates YAP [14] [15]. This inflammatory milieu also induces DNA damage and epigenetic alterations, fostering metaplasia and adenocarcinoma [16]. Studies in *H. pylori*-infected gastric organoids demonstrate enhanced stem cell-like properties, driven by HIPPO dysregulation, which precede malignant transformation [17].

4. Regulatory Mechanisms of the HIPPO Pathway in *H. pylori*-Associated Gastric Cancer

H. pylori disrupts the HIPPO pathway through direct, epigenetic, and indirect

mechanisms, amplifying oncogenic potential.

4.1. Direct Interactions with Virulence Factors

CagA interacts with PAR1b, disrupting epithelial polarity and inhibiting LATS1/2, leading to YAP nuclear translocation [18]. *In vitro* studies show CagA-dependent YAP activation induces EMT markers like Slug and Twist, promoting metaplasia in gastric epithelial cells [19]. VacA enhances this effect by stabilizing YAP through reduced proteasomal degradation [20]. Organoid models confirm that *H. pylori* strains with high CagA expression significantly upregulate YAP/TAZ, correlating with increased proliferation and stemness [21].

4.2. Epigenetic Modifications

H. pylori induces aberrant DNA methylation, notably via TET1, upregulating genes like GNB4 that activate the HIPPO-YAP1 axis [22]. Hypermethylation of tumor suppressor genes (e.g., RUNX3) and hypomethylation of oncogenes sustain YAP expression [23]. Histone modifications, such as H3K27 acetylation, further enhance YAP/TAZ-driven transcription, with studies showing persistent epigenetic changes post-*H. pylori* eradication [24]. These alterations create a permissive environment for tumor progression, particularly in chronic infections.

4.3. Crosstalk with Other Pathways

The HIPPO pathway interacts with multiple signaling cascades exacerbated by *H. pylori*. YAP/TAZ stabilize β-catenin in the Wnt pathway, upregulating MYC and cyclin D1, which drive cell cycle progression [25]. NF-κB activation by *H. pylori*-induced inflammation inhibits LATS, promoting YAP activity and inflammatory gene expression [26]. STAT3, activated by IL-6 in the tumor microenvironment, forms a feedforward loop with YAP, enhancing tumor growth and immune evasion [27]. These interactions amplify oncogenic signaling, with YAP acting as a hub for pathway convergence in *H. pylori*-positive GC.

4.4. Role in EMT and Metaplasia

LATS2 downregulation by *H. pylori* facilitates EMT, with YAP upregulating mesenchymal markers (e.g., vimentin, N-cadherin) and transcription factors (Slug, Twist) [28]. This process drives intestinal metaplasia, a precancerous lesion, with studies showing YAP overexpression in metaplastic tissues from *H. pylori*-infected patients [29]. Single-cell RNA sequencing reveals that YAP/TAZ activation in epithelial stem cells promotes a dedifferentiated state, linking chronic infection to early carcinogenesis [30].

5. Therapeutic Targets in the HIPPO Pathway

Targeting the HIPPO pathway offers promising avenues for *H. pylori*-associated GC, with strategies focusing on YAP/TAZ inhibition, kinase activation, and combination therapies. The following table summarizes key HIPPO-targeted agents,

their mechanisms, and development stages:

Agent	Mechanism of Action	Development Stage
Verteporfin	Disrupts YAP-TEAD interaction	Preclinical (GC cell lines, xenografts)
VT3989	Inhibits TEAD activity	Phase I clinical trials (GI cancers)
VGLL4-mimicking peptide	Blocks YAP-TEAD binding	Preclinical (*in vitro* studies)
Statins	Activates MST1/2 and LATS1/2, and promotes YAP phosphorylation	Clinical (repurposed, observational data)
Metformin	Inhibits YAP nuclear localization via AMPK	Clinical (observational, reduced GC risk)
USP12 inhibitors	Promotes YAP ubiquitination	Preclinical (GC cell lines)
BET inhibitors	Disrupts YAP-driven transcription	Preclinical (diffuse-type GC)
YAP-targeted siRNA	Silences YAP expression via nanoparticle delivery	Preclinical (ongoing studies)

5.1. Preclinical Data

Verteporfin, a small molecule inhibitor, disrupts YAP-TEAD interactions, reducing tumor growth in GC cell lines and xenografts [31]. Peptide-based antagonists mimicking VGLL4 block YAP-TEAD binding, offering a targeted approach with reduced off-target effects, showing suppression of proliferation and metastasis in *H. pylori*-infected models [32]. USP12 inhibitors target YAP stability by promoting its ubiquitination, demonstrating efficacy in GC cell lines [33]. BET inhibitors, which disrupt YAP-driven transcription, are effective in diffuse-type GC with high Galectin-3 expression [34]. Nanotechnology-based delivery systems, including YAP-targeted siRNA nanoparticles, enhance specificity and reduce systemic toxicity, with ongoing studies exploring their use in *H. pylori*-associated GC [35].

5.2. Clinical Trials

Repurposed drugs like statins activate MST1/2 and LATS1/2, restoring YAP phosphorylation, with clinical data suggesting reduced GC risk in treated patients [36]. Metformin, an AMPK activator, inhibits YAP nuclear localization, with observational studies indicating lower GC incidence in diabetic patients [37]. Combining *H. pylori* eradication with YAP inhibitors, such as clarithromycin-based therapy paired with verteporfin, reduces YAP-driven proliferation in mouse models and is under investigation in early-phase trials [38]. Clinical trials are also evaluating HIPPO modulators with checkpoint inhibitors, leveraging YAP's role in immune suppression to enhance immunotherapy outcomes in GC [39]. Preclinical studies of IAG933, a novel YAP-TEAD inhibitor, demonstrate potent inhibition of tumor growth in gastric carcinoma models, such as HER2-amplified NCI-N87 xeno-

grafts, particularly when combined with trastuzumab, highlighting its potential for *H. pylori*-associated GC [40].

6. Conclusion and Future Directions

The HIPPO pathway's dysregulation is a cornerstone of *H. pylori*-driven gastric carcinogenesis, mediating the transition from infection to malignancy through complex molecular and epigenetic mechanisms. Targeting YAP/TAZ and upstream regulators offers transformative potential, with emerging therapies like verteporfin, statins, and novel inhibitors showing promise in preclinical and early clinical studies. However, strain heterogeneity in *H. pylori* virulence factors, such as variable CagA expression, and host genetic polymorphisms affecting inflammatory responses may influence HIPPO activation and therapeutic outcomes, complicating standardized treatments. These limitations underscore the need for personalized therapeutic strategies. Despite progress, challenges persist in targeting the HIPPO pathway. YAP/TAZ inhibitors often face resistance due to compensatory pathways, such as EGFR or PI3K activation [41]. Biomarker development is critical to identify patients likely to benefit from HIPPO-targeted therapies, with YAP nuclear localization and TEAD4 expression proposed as candidates [42]. Multi-omics approaches, integrating genomics, epigenomics, and transcriptomics, can uncover novel targets and resistance mechanisms [43]. Artificial intelligence-driven modeling of HIPPO interactions could optimize drug design and predict therapeutic responses [44]. Future research should focus on personalized medicine, combining HIPPO inhibitors like IAG933 with *H. pylori* eradication and immunotherapy to address tumor heterogeneity and improve outcomes, with preclinical studies paving the way [45].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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