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INFLAMMATION, IMMUNITY & VACCINES

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Abstract – *Helicobacter pylori* has co-evolved with humans to infect the stomach mucosa persistently. *H. pylori* infection is the most prevalent chronic bacterial infection in humans. It causes chronic-active gastritis in all infected individuals and is the leading etiologic agent for the development of peptic ulcer disease and gastric cancer. Understanding *H. pylori*-driven host responses is key to preventing and treating *H. pylori*-associated disease. The past year has seen significant progress in unlocking *H. pylori* inflammatory mechanisms, immune regulation, and novel prophylactic strategies. This review summarizes the most important publications from April 2024 to March 2025 and discusses their implications for understanding *H. pylori* pathogenesis and the future development of effective vaccines.

Keywords: *Helicobacter pylori*, Immunity, Inflammation, Gastritis, Gastric cancer, Vaccine.

INTRODUCTION

Helicobacter pylori induces chronic inflammation of the gastric mucosa in all infected individuals and is the major risk factor for gastroduodenal ulcers and intestinal-type gastric cancer. *H. pylori* is specifically adapted to colonize the gastric epithelium in the acidic environment of the stomach. The infection causes chronic active gastritis with infiltration of neutrophils and macrophages and induces strong cellular and humoral immune responses. However, *H. pylori* exploits a wide range of mechanisms to skew host responses toward a tolerogenic phenotype and to escape eradication by the immune system[1].

Chronic mucosal infection drives gastric carcinogenesis, making *H. pylori* the leading infectious carcinogen, responsible for approximately 750.000 gastric cancer cases each year. To date, systematic screening and antibiotic eradication of the infection are the only prevention strategies against gastric cancer. However, population-wide antibiotic use for cancer prevention raises concerns about antimicrobial stewardship, while resistance rates of *H. pylori* have been rising alarmingly over recent decades[1]. Therefore, there is an urgent clinical need for a vaccine against *H. pylori*. Nevertheless, all attempts to develop a drug inducing durable protective immunity against *H. pylori* have failed so far. These efforts, in turn, have provided important insights into *H. pylori* immune evasion and cellular and humoral correlates of protection[2].

This article summarizes relevant literature on *H. pylori* inflammation, immunity, and vaccine development from the past year. We performed a systematic PubMed search for literature published between April 2023 and March 2024 using a comprehensive set of keywords related to *Helicobacter pylori*, inflammation, immunity, cytokines, and vaccination. The search strategy included terms for key immune cell populations (e.g., T cells, B cells, NK cells, macrophages, dendritic cells), inflammatory mediators (e.g., interleukins, cytokines, chemokines), and vaccination, and restricted results to English-language original research articles. Reviews, case reports, and other non-primary publications were excluded. The identified studies were screened for quality and relevance by abstract review, assessment of overlapping findings, and consideration of journal reputation. Selected publications were then grouped into three thematic sections — inflammation, immunology, and vaccines — to provide an overview of recent advances in *H. pylori* research during this period.

INFLAMMATION

Innate Immune Signaling and Macrophages in *H. pylori* Gastritis

H. pylori infection elicits a strong innate immune response. Activation of innate immune signaling leads to the secretion of multiple pro-inflammatory cytokines and chemokines important for the recruitment of innate immune cells such as neutrophils and macrophages to the gastric mucosa. At the population level, genetic variation in innate immune signaling pathways has been linked to gastric pathology and cancer risk associated with *H. pylori* infection[3]. Kim et al[4] highlighted sex differences in gastric pathology associated with polymorphisms in cytokine genes in the context of *H. pylori* infection, namely *IL-1B* and *IL-8*. For IL-1B, only male carriers of the IL-1B-511 CC variant had an increased risk of advanced atrophic lesions compared to CT and TT carriers (HR, 4.377; 95% CI, 1.387-13.814). For IL-8, two alleles of the IL-8-251 polymorphism were associated with different outcomes in males and females. In women, the IL-8-251 AA variant was associated with advanced atrophic gastritis compared to AT and TT carriers (HR, 3.799; 95% CI, 1.515-9.523), while in men, the IL-8-251 TT variant was associated with intestinal metaplasia (HR, 3.128; 95% CI, 1.149-8.512)[4].

Macrophages are pivotal innate immune cells that drive the inflammatory response in *H. pylori* gastritis. At the same time, they are manipulated by the bacterium to evade immune clearance[5]. Given the important role of macrophages in the immune response against *H. pylori*, identifying the regulatory mechanisms that drive their recruitment to the stomach and ultimately determine their polarization is crucial. In the last year, several publications have reported new mechanisms of interaction between macrophages and *H. pylori*. The Busada group[6] presented new findings on the role of endogenous glucocorticoids in macrophage-mediated gastric mucosal homeostasis. They had previously shown that adrenalectomy in mice resulted in a rapid onset of spontaneous gastric inflammation, oxyntic atrophy, and spasmolytic polypeptide-expressing metaplasia (SPEM). This effect did not depend on lymphocytes but instead on infiltrating monocytes[6]. In the new study, they used mice with conditional knockout of the glucocorticoid receptor in the myeloid lineage. Using this model, the authors confirmed that glucocorticoid signaling in macrophages is required for their normal activation by inflammatory stimuli. However, after *H. pylori* and *H. felis* infection, glucocorticoid receptor-deficient mice showed impaired gastric immune responses, with reduced T-cell recruitment and protection against atrophic gastritis and the development of pyloric metaplasia. These findings appear to contradict previous data[7], leading the authors to propose a dual role for glucocorticoid signaling – preparing macrophages to respond to bacterial infection while limiting their pathogenic activation.

The chemokine CCL3 (MIP-1α) is known for attracting monocytes and macrophages to sites of infection. Wei et al[8] recently demonstrated that CCL3 is induced by *H. pylori* and contributes to gastric mucosal injury in *H. pylori*-associated gastritis. The expression of CCL3 is regulated by the JAK1/STAT1 signaling pathway in macrophages and directly drives epithelial barrier disruption through p38 phosphorylation *in vitro* and *in vivo*[8].

The spatial interaction of *H. pylori* with innate immune cells is also an important aspect for understanding the pathology of inflammation. In this regard, Ishikawa-Ankerhold et al[9] pioneered visualization of interactions between *H. pylori* and neutrophils and macrophages in the mouse stomach using multiphoton *in situ* imaging. This intravital imaging model promises new, dynamic insight into interactions between pathogens and immune cells *in vivo*[9].

Finally, inhibition of the recruitment and activation of macrophages represents a potential approach to reduce gastric inflammation during *H. pylori* infection. Fei et al[10] demonstrated that the TNF/TNFR1 signaling axis regulates NLRP3 inflammasome activation in *H. pylori*-infected macrophages *in vitro* and *in vivo*, promoting M1 macrophage polarization and gastric inflammation. Blocking TNF/TNFR1 signaling, either pharmacologically or genetically, reduced NLRP3 activation and M1 polarization, resulting in reduced production of inflammatory cytokines *in vitro*[10]. Reduced inflammation was also observed in a study[11] using a compound that selectively antagonizes NOD1. Based on previous findings on the role of NOD1 signaling in *H. pylori* gastritis and carcinogenesis, Liu et al[11] developed a small molecule to selectively antagonize NOD1. The compound showed potent inhibition of CXCL1 and CXCL8, which are involved in the recruitment of immune cells in *H. pylori* infection, and of the pro-inflammatory cytokines IL-6 and TNFα *in vitro*. Likewise, the levels of IL-6 and CXCL1 in the stomach tissue were reduced in *H. pylori*-infected mice after treatment with the NOD1 inhibitor[11].

INFLAMMATION-DRIVEN GASTRIC CARCINOGENESIS

Chronic mucosal inflammation induced by *H. pylori* may progress to oxyntic atrophy and intestinal metaplasia, a preneoplastic stage preceding gastric cancer[12]. Autoimmune gastritis has a different etiology and is characterized by a specific host immune response against the proton pump expressed by gastric parietal cells, and by inflammation restricted to the stomach corpus. However, it also leads to oxyntic atrophy, intestinal metaplasia, and an increased risk of gastric cancer. However, the distinctions between metaplastic cells in both types of gastritis and their respective cancer risks have remained unclear. Using histopathologic analyses and single-cell transcriptomics of mouse models and human stomach samples, Hoft et al[13] showed that both gastritis types induce several subtypes of gastric metaplasia, but none were specific to either etiology. Of note, the authors identified one cancer-associated subtype in both groups that resembled incomplete intestinal metaplasia and was characterized by the biomarker alanyl aminopeptidase N (ANPEP)/CD13[13]. Current guidelines already recommend close surveillance of patients with incomplete intestinal metaplasia[14]. However, the diagnosis of this entity is challenging and not standardized, indicating potential use of this biomarker for risk stratification in gastritis.

Macrophages play key roles in the immune response against *H. pylori* and, when reprogrammed to an M2 phenotype, support cancer progression. In contrast to pro-inflammatory M1 macrophages, M2 macrophages exhibit an anti-inflammatory and tissue-repair phenotype, promoting immune evasion, angiogenesis, and tumor progression[15]. Two recent studies[16,17] investigated the role of M2 macrophages in gastric cancer. First, using Gene Expression Omnibus (GEO) datasets, Yang et al[16] identified CD14 as the only gene upregulated in both *H. pylori* gastritis and gastric cancer. High CD14 expression is associated with higher tumoral M2 macrophage infiltration and better response to anti-CTLA-4 checkpoint inhibitor therapy. These findings were reproduced in a mouse model of MNU-induced gastric cancer, which similarly showed increased CD14 expression and M2 infiltration[16]. In the second study[17], by analyzing the Cancer Genome Atlas (TCGA) dataset, Yu et al[17] confirmed increased IL-6 expression in gastric cancers compared to normal stomach samples and an association with reduced survival in patients with IL-6-high cancers. It is well established that the IL-6-gp130-STAT3 signaling pathway is pivotal in gastric inflammation and carcinogenesis[18]. IL-6 levels were correlated with the expression of the M2 macrophage marker CD163. These findings were further explored in *vitro* experiments, where stimulation with *H. pylori* induced an autocrine and paracrine feed-forward loop of IL-6 expression in macrophages and gastric epithelial cells[17].

IMMUNITY

Th17 Immunity in *H. pylori* Gastritis

During *H. pylori* infection, Th17-derived IL-17 serves as a key link between innate and adaptive immunity by orchestrating neutrophil recruitment and inflammatory responses, while also promoting B-cell activation and T follicular helper cell differentiation[19].

The Algood group continued its previous work on IL-17 signaling in *H. pylori* infection. They observed that IL-17RA knockout mice developed severe gastric hyperinflammation and showed reduced *H. pylori* colonization, and that T cell–specific IL-17RA deficiency was not sufficient to reproduce this phenotype[20,21]. Using a novel gastric epithelial cell–specific IL-17RA knockout mouse model, the authors demonstrated that IL-17RA signaling in gastric epithelial cells is critical to restrain excessive IL-17–driven inflammatory responses to *H. pylori* infection. These epithelial-specific knockout mice exhibited pronounced neutrophilic infiltration in the gastric mucosa that was not present in germline IL-17RA knockout mice. Further experiments identified gastric fibroblasts as a major cell type producing CXCL1, CXCL2, and CXCL5 in response to IL-17 stimulation, indicating that gastric epithelial cells are not the sole source of neutrophil-recruiting chemokines[22].

Richter et al[23] built on the emerging concept that bitter taste receptors (TAS2Rs) are expressed in multiple tissues outside the oral cavity, where they can modulate immune responses and host metabolism, e.g., in the small intestine[24]. The authors demonstrated that gastric digestion of the sweet-tasting protein thaumatin (E 957) releases bitter peptides that, upon activation of TAS2R16, reduce *H. pylori*-induced IL-17A secretion by up to 90%. Despite being a limited proof-of-concept *in vitro* study, this work suggests novel links between environmental factors, diet, and the pathogenesis of *H. pylori* infection[23].

Immune Tolerance to *H. pylori*

IgA is considered a key mediator of mucosal immunity against bacterial and viral pathogens. By comparing mice infected with *Citrobacter rodentium* and *H. pylori*, the Artola-Boran et al[25] demonstrated an unexpected role for IgA in *H. pylori* infection. Both infections elicited a strong local IgA response and bacterial coating with IgA. IgA induction against *H. pylori* depended on a functional type IV secretion system and CagA. $IgA^{-/-}$ mice were unable to control *C. rodentium* colonization and showed excessive colitis. However, $IgA^{-/-}$ mice infected with *H. pylori* showed lower levels of colonization. Ablation of the complement component C3 restored high-level *H. pylori* colonization in these mice, indicating that IgA facilitated the persistence of *H. pylori* by preventing complement activation. Intriguingly, infecting $IgA^{-/-}$ offspring with *H. pylori* and nursing them with wild-type mothers (and vice versa; litter-swap experiment) reversed the phenotype of $IgA^{-/-}$ offspring, indicating that maternally derived IgA in breast milk may promote *H. pylori* tolerance in newborns[25]. Tolerance to *H. pylori* may even be transmitted *in utero:* Wei et al[26] showed that *H. pylori* outer membrane vesicles (OMV) were able to cross the placental barrier and induce a reprogramming of T-cell subsets towards a regulatory phenotype in the thymus and peripheral blood of fetal mice. This represents the first demonstration of intrauterine immune priming *via* maternal-fetal transmission of *H. pylori* components. It is tempting to speculate that intrauterine induction of central tolerance to *H. pylori* might pave the way for postnatal transmission of *H. pylori* infection from mothers to newborns[26].

Induction of regulatory T (Treg) cells is a hallmark of *H. pylori* infection and a major mechanism supporting bacterial persistence. The protein Angiopoietin-like 4 (ANGPTL4) was recently described as inducing Treg cells through two distinct mechanisms[27]. ANGPTL4 is a member of the ANGPTL protein family and does not bind the ANGPT receptor TIE1/2. This protein has been implicated in a wide spectrum of metabolic and inflammatory diseases and cancers[28]. Xie et al[27] observed increased ANGPTL4 expression in *H. pylori*-infected gastric mucosa of humans and mice. ANGPTL4 was synergistically induced in gastric epithelial cells by *H. pylori* in a CagA-dependent manner. Interestingly, $Il17a^{-/-}$, $Angptl4^{-/-}$, and $Il17a^{-/-}Angptl4^{-/-}$ double-knockout mice showed attenuated bacterial colonization and gastric inflammation. Treatment with ANGPTL4 increased bacterial burden and Treg cell accumulation, while decreasing neutrophil infiltration. Mechanistically, the authors showed that ANGPTL4 bound to Integrin subunit αV (ITGAV) on gastric epithelial cells, resulting in ERK inhibition and suppression of Claudin-1 and CXCL1, leading to reduced neutrophil infiltration. At the same time, ANGPTL4 binding to ITGAV on monocytes promoted CCL5 production and the accumulation of Treg cells. ANGPTL4 also directly stimulated Treg cell proliferation *via* ITGAV and NF-κB during *H. pylori* infection. Overall, the authors propose a model in which ANGPTL4 collectively promotes *H. pylori* colonization and inflammation[27].

VACCINES AGAINST *H. PYLORI*

As antibiotic resistance rates in *H. pylori* are rising and eradication therapy is increasingly challenged, updated therapy regimens are needed. Therefore, vaccination may become a key component of future eradication strategies.

In Silico Vaccine Design

The identification of immunogenic antigens is crucial for the success of a vaccine. Several *in silico* models have been developed in recent years to aid in the search for novel antigen combinations. Most commonly, preventive and therapeutic vaccines with a multi-epitope approach are proposed. Targeted proteins usually include virulence factors of *H. pylori*, such as CagA[29,30], VacA[30], or urease[29,30], and outer membrane proteins (OMP), such as HopE[29], BabA[29-31], and SabA[29-31]. *In silico* studies usually involve predictions of immune cell epitopes, secondary and tertiary structure, physicochemical properties, and molecular docking to host cells. Efficacy is primarily estimated through immunogenicity assays, estimating the induction of interleukins (IL-4, IL-10) and IFN-γ[29,30]. However, experimental validation of the proposed vaccines often remains outstanding under laboratory conditions.

DNA Vaccines

DNA vaccines have been shown to be a simple and effective approach to induce broad-based immune responses. Several studies have assessed the immunogenicity and efficacy of DNA vaccines encoding bacterial virulence factors as antigens. Amaral et al[32] engineered new multi-epitope, recombinant protein–based and plasmid DNA (pDNA–) based vaccines against *H. pylori*. *H. pylori* antigens and virulence factors, including CagA, GroEL, HpaA, HomB, UreB, and VacA, were produced, encapsulated in chitosan nanoparticles, and administered orally and intramuscularly to female BALB/c mice. Serum levels of antigen-specific IgG1 and IgG2 increased significantly after intramuscular administration of the pDNA-based and recombinant protein-based vaccines. Oral administration of either vaccine caused a significant increase in secreted mucosal IgA (sIgA), indicating a mucosal immune response[32]. Azami et al[33] also synthesized a novel multi-epitope DNA-based vaccine against *H. pylori*, targeting four antigenic proteins, including outer membrane protein HofA, Hcp β-lactamase–like protein, an outer membrane β-barrel, and an outer membrane β protein. Female BALB/c mice that received intramuscular vaccination showed a significant increase in cytokines (IFN-γ, IL-1β) and antigen-specific IgG antibodies compared to controls, demonstrating immunogenicity[33]. However, efficacy studies were not performed using these two approaches. Consequently, the effectiveness in protecting against *H. pylori* infection remains to be corroborated.

Chaleshtori et al[34] immunized BALB/c mice with a pDNA vaccine targeting the *H. pylori* virulence factor LeoA. The DNA vaccine was encapsulated in chitosan nanoparticles. Immunization induced a significant increase in LeoA-specific IgG. The effectiveness of the vaccination was assessed by counting colony-forming units in the stomachs of *H. pylori*-challenged mice. The immunized mice showed a significantly lower gastric *H. pylori* burden compared to controls[34].

Live Carrier Vaccines

Live carrier vaccines are an alternative vaccination strategy, typically employing attenuated bacteria as vectors for antigen presentation. Bacteria that are generally recognized as safe (GRAS) represent a nonpathogenic alternative to attenuated microorganisms. In this context, Ni et al[35] produced two recombinant *Lactococcus lactis* (GRAS) live carrier vaccines expressing either UreA antigen or UreA antigen fused to the *Escherichia coli* heat-labile toxin B subunit. Orally immunized BALB/c mice showed a significant increase in sIgA compared to controls. However, IgG levels were not significantly increased. Vaccination caused a significant increase in IFN-γ and IL-17A. In efficacy testing, BALB/c mice prophylactically immunized with either vaccine showed significantly lower *H. pylori* colonization compared to controls, as assessed by quantitative culture[35].

OUTER MEMBRANE VESICLES AND BACTERIUM-LIKE PARTICLES

Other strategies used to generate an effective *H. pylori* vaccine include the use of bacterium-like particles (BLP) and outer membrane vesicles (OMV). In particular, OMVs are a well-established vaccine platform for combating bacterial pathogens such as *Neisseria meningitidis*[36]. Because OMVs can naturally present antigens and trigger immune responses, they represent a promising approach in vaccine development[37]. BLPs, on the other hand, consist of nonliving bacterial components that are also capable of inducing host immune responses. Protection studies using BLPs are often performed in viral disease models, such as influenza and respiratory syncytial virus[38].

Zhang et al[39] investigated the adaptive immune response to an *H. pylori* multi-epitope purified antigen delivered together with BLPs derived from *Lactococcus lactis*, as a novel microfold (M) cell–targeted vaccine. The multi-epitope antigen contained pathogenic *H. pylori* adhesion factors, such as CagL, HpaA, Lpp20 and urease. Male BALB/c mice were orally immunized and assessed for immune responses. Vaccinated mice showed significantly higher IgG and sIgA levels. IL-4-, IL-17A, and IFN-γ levels increased significantly. Infected mice treated with the vaccine showed significantly lower gastric *H. pylori* loads and reduced gastric damage[39].

Liu et al[40] showed that OMVs of *Salmonella enterica* serovar *Typhimurium* deficient in outer membrane protein A (OmpA) were potent vaccine candidates when presenting the CagA and UreB antigens. Female C57BL/6 mice intragastrically immunized with *H. pylori* antigen–presenting OMVs showed significantly higher IgG and IgA levels and lower urease activity and *H. pylori* loads compared to controls. Additionally, significant increases in IL-4, IL-12, and IL-17 levels were observed, indicating Th1 and Th2 stimulation[40]. In a subsequent study[41], the same authors designed a recombinant OMV-based vaccine in which engineered OMVs both presented CagA, UreB, and VacA and carried lipopolysaccharide (LPS) that had been modified by knockdown of *H. pylori* immune-evasion genes (lpxE, lpxF, futB). Female C57BL/6 mice immunized with the vaccine prior to *H. pylori* challenge had significantly lower urease activity and gastric *H. pylori* burden than control-treated mice. Cytokine levels, including IL-4, IL-12, IL-13, IL-17, IFN-γ, as well as IgG and sIgA levels, were significantly increased. Flow cytometry showed that vaccination with LPS-altered OMVs caused a significant increase in $CD4^+CD154^+$ T cells, $CD4^+CD154^+IFN\text{-}\gamma^+$ T cells, and $CD4^+CD154^+IL\text{-}17A^+$ T cells compared to treatment with wild-type control OMVs[41].

In conclusion, these results show that *H. pylori* vaccination is progressing. In particular, multi-epitope targeting approaches appear especially promising. Future work should include the evaluation of supportive vaccine adjuvants.

CONCLUSIONS

The past year has provided important insights into how *H. pylori* shapes gastric inflammation, immune responses, and prospects for prevention. New studies highlight the complexity of innate immunity, with macrophages and neutrophils emerging as central players that can either promote or restrain pathology depending on their signaling context. Advances in imaging and mechanistic analyses revealed dynamic host–pathogen interactions and identified novel therapeutic targets, such as the NOD1 and TNF/TNFR1 pathways, that could mitigate gastritis. At the same time, inflammation-driven carcinogenesis remains a concern, with recent work elucidating metaplastic subtypes and macrophage polarization pathways that fuel tumor progression, while also identifying biomarkers for risk stratification. On the adaptive side, recent work has deepened understanding of Th17 responses, IgA-mediated tolerance, and regulatory networks such as ANGPTL4, which collectively underscore the finely tuned balance between immunity and persistence. Interestingly, maternal and environmental influences — including breast milk antibodies, *in utero* exposure to bacterial vesicles, and dietary peptides — were shown to shape long-term susceptibility to *H. pylori*. Finally, momentum in vaccine development is accelerating, with multi-epitope constructs, live carriers, OMVs, and *in silico*-designed candidates showing promise in preclinical models. While none are yet clinically validated, these efforts signal a renewed optimism for effective immunization strategies. Together, these discoveries advance our mechanistic understanding of *H. pylori* pathogenesis and outline potential translational avenues for improved diagnostics, therapeutics, and ultimately preventive vaccination.

Conflicts of Interest

The authors declare no conflicts of interest.

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Authors' Contributions

Conceptualization: LM, RML. Methodology (search strategy): LM, JW. Investigation (literature review): LM, JW. Data curation (reference management): LM, JW. Writing – Original Draft: LM, JW, RML. Writing – Review & Editing: LM, JW, RML. Supervision: RML. Project administration: LM.

Data Availability Statement

No new data were generated or analyzed in this study.

AI-Generated Content Disclosure

Artificial intelligence was used for language refinement.

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