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Innate Immunity in *Helicobacter pylori* Infection and Gastric Oncogenesis

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ABSTRACT

Helicobacter pylori is an extremely common cause of gastritis that can lead to gastric adenocarcinoma over time. Approximately half of the world's population is infected with *H. pylori*, making gastric cancer the fourth leading cause of cancer-related deaths worldwide. Innate immunity significantly contributes to systemic and local immune responses, maintains homeostasis, and serves as the vital link to adaptive immunity, and in doing so, mediates *H. pylori* infection outcomes and consequent cancer risk and development. The gastric innate immune system, composed of gastric epithelial and myeloid cells, is uniquely challenged by its need to interact simultaneously and precisely with commensal microbiota, exogenous pathogens, ingested substances, and endogenous exfoliated cells. Additionally, innate immunity can be detrimental by promoting chronic infection and fibrosis, creating an environment conducive to tumor development. This review summarizes and discusses the complex role of innate immunity in *H. pylori* infection and subsequent gastric oncogenesis, and in doing so, provides insights into how these pathways can be exploited to improve prevention and treatment.

1 | Introduction

Gastric adenocarcinoma is a leading cause of cancer-related deaths globally, especially in Eastern and Southeast Asia [1], and its prognosis is often poor [2]. Infective pathogens of the mucosa are well-established drivers of gastric oncogenesis and development. Chronic infections can alter normal gene expression, attenuate host immune responses, and evade immune killing. Furthermore, certain bacteria and viruses can disrupt cellular pathways associated with key biological processes, such as proliferation and resistance to apoptosis, that are hallmarks of cancer [3].

Helicobacter pylori, designated a group I carcinogen [4] is the primary causative agent for gastric adenocarcinoma [5]. *H. pylori* colonizes the stomach long-term despite protective mucosal immunity and its barrier function, leading to epithelial cell injury and complex inflammation mediated by multiple immune mechanisms that constitute chronic gastritis [6, 7]. Moreover, *H. pylori* infection is challenging for the host to eradicate, and most infections become chronic [8, 9].

H. pylori infected our human ancestors as far back as 60,000 years ago. The interactions between and co-evolution of humans and

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H. pylori have diversified *H. pylori* strains and influenced the development of the human immune system, particularly innate immunity [10–12]. Innate immunity usually serves as the primary defense mechanism against external pathogens, and it is characterized by rapid and non-specific responses that bridge to other more elaborate and robust adaptive immune responses. *H. pylori* possess various conserved components such as lipopolysaccharide (LPS), flagellin A (FlaA), fucose, and DNA or single-stranded RNA (ssRNA), which are effectively identified by the innate immune system, triggering a cascade of immune responses. These inflammatory responses include vascular dilation, increased vascular permeability, and mobilization of immune cells to attack and prevent the spread of invading pathogens [13].

Despite robust innate immunity, there is growing evidence that *H. pylori* has evolved complex mechanisms to bypass the human immune defense system, thereby establishing chronic infection to increase the risk of neoplasia [14–16]. Furthermore, the antibiotic resistance of *H. pylori*, particularly to macrolides, is rapidly increasing, reaching or exceeding high-level macrolide resistance thresholds in multiple regions, exacerbating cancer-related events and imposing a substantial burden on society and individuals [17].

Although the development of gastric cancer is multifactorial, as the leading etiological factor, it is important to understand the mechanisms by which *H. pylori* contributes, to gastric carcinogenesis. As the innate immune system mediates the first host-pathogen interactions on *H. pylori* infection, this represents a critical step paving the way for future oncogenic sequelae. Understanding these interactions is important for modifying pro-carcinogenic responses to the pathogen, especially in the face of increased antimicrobial resistance. This review therefore aims to comprehensively explore current knowledge on the interactions and crosstalk between *H. pylori* and innate immunity, particularly with respect to the gastric mucosa, and explore their contributions to oncogenesis.

2 | Roles of Innate Immunity in *Helicobacter pylori* Infection and Oncogenesis Within the Gastric Mucosa

The gastrointestinal tract is the largest lymphatic organ in the human body, housing 70%–80% of immune cells. Together with protective epithelial barriers, these elements form a comprehensive and dynamic defense system [18, 19]. Epithelial cells and immune cells within the lamina propria (granulocytes, mast cells, macrophages, neutrophils, B/T lymphocytes, and plasma cells [20]) are vital components of the gastrointestinal tract mucosa, whose primary functions include presenting antigens, provoking immune responses against external pathogens and stimuli, and promoting tolerance to prevent immune imbalance [21, 22]. When the host encounters exogenous or endogenous antigens, innate immune cells (such as macrophages, mast cells, dendritic cells [DCs], and innate lymphoid cells [ILCs]) are activated, recruited to reach target sites in the stomach, triggering appropriate inflammatory responses, amplifying immune reactions, and acting as a link to adaptive immunity. However, in some instances, and if maladapted, they can contribute to a pathological state, such as chronic inflammation and fibrosis. Gastric mucosa-associated lymphoid tissue (MALT), abnormal in adults, is often observed in chronic inflammation, such as that found in chronic *H. pylori* infection [23].

Despite susceptibility to pathogens, the gastrointestinal tract also hosts diverse bacterial communities which maintain host health through intricate interactions with mucosal immunity [21, 24]. The gastrointestinal microbiota has co-evolved with its mammalian hosts throughout evolution to perform vital roles such as digesting indigestible food, producing essential vitamins, defending against pathogens, and strengthening the host's immune system [25–28]. Indeed, microbiota colonization is crucial for immune system development and is present from early life [21, 29]. When the microbiota is absent, the host's ability to resist pathogens is weakened, leading to immune dysregulation and hypersensitivity to endogenous antigens, potentially resulting in autoimmune diseases. Interestingly, many of these disorders can be reversed by recolonizing the gut with commensal microbiota, especially early in life [30–33].

Given the continuous exposure of the gastrointestinal mucosa to countless external antigens, the immune system must rapidly and accurately distinguish between harmful and benign species and promptly initiate appropriate immune responses. These responses include activating pro-inflammatory or anti-inflammatory signaling pathways, as needed.

2.1 | Pattern Recognition Receptors

Protection against pathogens is largely mediated by the pattern recognition receptor (PRR) superfamily. PRRs can be broadly categorized into extracellular types, such as Toll-like receptors (TLRs), and intracellular types, such as nucleotide-binding oligomerization domain-like receptors (NLRs) and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) [34, 35]. The host's immune defense mechanisms are activated upon recognition of conserved biological components of exogenous microorganisms, referred to as pathogen-associated molecular patterns (PAMPs), or components of abnormal host cells, referred to as damage-associated molecular patterns (DAMPs). This recognition triggers downstream intracellular signaling pathways, such as the NF-κB pathway and inflammasomes, leading to the activation of genes responsible for the production of inflammatory cytokines, chemokines, costimulatory molecules, and antigen-presenting molecules [36]. This process initiates specific immune responses and recruits a diverse range of systemic immune cells.

2.1.1 | Toll-Like Receptors

Toll-like receptors (TLRs), a well-studied class of PRR, are widely expressed by epithelial and innate immune cells and serve a vital function in recognizing PAMPs [37]. Structurally, TLRs are composed of a leucine-rich repeat extracellular domain and a Toll/IL-1R homology domain. This structure enables them to specifically bind ligands and transmit signals via tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) and evolutionarily conserved signaling intermediate

in Toll pathways (ECSIT) [38]. These signaling events activate inflammatory cascades, primarily through the NF-κB and p38 MAPK pathways. Ten types of TLR have been identified in humans, with some present in gastric epithelial cells under both normal and pathological conditions [38]. TLRs are primarily located at the cell surface (TLR1, TLR2, TLR4, and TLR5) or within endosomes (TLR3, TLR7, TLR8, and TLR9), targeting extracellular and endocytosed microbial components, respectively [39]. Generally, TLRs are thought to induce and enhance inflammation and cellular proliferation during infection and oncogenesis. However, TLR9 can display either pro-inflammatory or anti-inflammatory functions, according to the specific microenvironment [40].

TLRs play a significant role in the immune response to *H. pylori* infection and can influence the development of gastric carcinogenesis [41]. Various components of *H. pylori*, such as LPS, peptidoglycan, and bacterial nucleic acids, serve as PAMPs recognized by specific TLRs. For example, TLR2 and TLR4 are key receptors that identify bacterial cell wall components like peptidoglycan and LPS [42]. Activation of TLRs by *H. pylori* PAMPs triggers the release of pro-inflammatory cytokines IL-1β and TNF-α, which are central to initiating and sustaining the inflammatory response [43]. Additionally, TLR-mediated inflammation can modulate the activation and differentiation of T helper cell subsets, such as Th1 and Th17 cells, involved in immune defense against *H. pylori* [44]. TLRs can also indirectly impact the development of adaptive immune responses by affecting the functions of antigen-presenting cells (APCs).

However, while TLR-mediated immune responses are crucial for controlling infection, chronic TLR activation due to persistent *H. pylori* infection can lead to sustained inflammation [45]. Chronic inflammation further creates an environment conducive to developing gastric cancer by promoting DNA damage, mutations, and tissue remodeling [46]. Certain TLR gene polymorphisms (e.g., in *TLR2* and *TLR4*) have been associated with increased susceptibility to *H. pylori* infection and gastric cancer. Additionally, TLRs are expressed on gastric epithelial cells and can influence their responses to *H. pylori* infection by producing pro-inflammatory cytokines and chemokines, contributing to the overall immune response of the gastric mucosa [47].

In summary, TLRs play a dual role in *H. pylori* infection and gastric carcinogenesis. They are essential for recognizing and responding to *H. pylori* infection and initiating protective immune responses; however, chronic TLR-mediated inflammation can contribute to the development of gastric cancer by promoting a pro-oncogenic environment.

2.1.2 | Nucleotide-Binding Oligomerization Domain-Like Receptors

NLRs act as intracellular receptors or sensors that form a multiprotein complex known as the inflammasome with adaptor and effector proteins. In mammals, the NLR family consists of: [1] the NOD family, including NODs 1–5 and the class II major histocompatibility complex (MHC) transcription activator (CIITA); [2] the NLRP family, including NLRPs 1–14; and [3] the ICE protease-activating factor (IPAF) subfamily [48, 49]. The primary function of NLRs is to precisely recognize PAMPs to facilitate the maturation of downstream effector molecules, ultimately driving inflammation and cell death. The NLRP3 inflammasome has an essential function in the stomach. Recognition of specific ligands triggers oligomerization of the receptor protein, which binds to the N-terminal pyrin domain of the apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC). This interaction leads to the recruitment and activation of the downstream effector protein, pro-caspase-1. Ultimately, this process leads to cleavage and activation of pro-inflammatory cytokines such as IL-1β and IL-18 [38].

NLRs contribute to both protective and pathological responses in the stomach, particularly through detection of *H. pylori* via its peptidoglycans. Specifically, NLRs such as NOD1 and NOD2 recognize bacterial peptidoglycan fragments, triggering downstream immune responses [50]. Upon recognition of *H. pylori* components, NLRs activate signaling pathways that produce pro-inflammatory cytokines such as IL-1β and TNF-α, which play powerful roles in clearing invasive *H. pylori* [51]. NLR activation can also lead to the recruitment of immune cells, including neutrophils and macrophages, to the site of infection, enhancing the immune response and bacterial clearance [52]. NLRs also play a crucial role in resolving inflammation. Typically, NLR activation induces anti-inflammatory cytokines like IL-10, which are vital for balancing the immune response and preventing excessive tissue damage [53]. Interestingly, certain NLR gene variants have been associated with a higher risk of gastric cancer development in individuals infected with *H. pylori* [35, 54]. These genetic variants can impact the activation of NLR-associated signaling pathways and influence their inflammatory effects during infection. NLRs are also implicated in DNA damage responses, as their activation can significantly increase the production of reactive oxygen species (ROS) and DNA-damaging agents, fueling inflammation and oncogenesis [55].

Several authors have proposed specific mechanisms by which NLRs contribute to gastric oncogenesis. When induced by LPS, gastric epithelial cells increase expression of CD209, which interacts with TLR4 to activate the NLRP3 inflammasome via a MyD88-independent pathway, provoking inflammation [56]. Li et al. demonstrated that NLRP3 enhances gastric epithelial cell proliferation and tumorigenesis by binding to the cyclin D1 promoter and promoting its transcription. Meanwhile, *H. pylori* infection can augment NLRP3 expression while suppressing miR-22, a constitutive microRNA suppressor of NLRP3, exacerbating this process [57]. Castaño-Rodríguez et al. corroborated these findings in cohorts of Chinese patients with noncardia gastric cancer, revealing a synergistic interaction between NLRs and *H. pylori* in gastric oncogenesis and development [54]. Conversely, inhibitors such as caspase-1 inhibitors (AC-YVAD-CMK), genipin, C-phycocyanin, and fucoidan have shown promise in attenuating inflammation by inhibiting NLRP3 inflammasome-related effects. These interventions provide valuable protection in mouse models of ethanol-induced acute gastric injury, highlighting the potential of this pathway as a target for drug development [58–61].

2.1.3 | Retinoic Acid-Inducible Gene I-Like Receptors

As a type of cytoplasmic PRR, retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) are primarily composed of a central DExh-box-type RNA helicase domain, responsible for signal transduction, and a C-terminal domain, which recognizes immunogenic RNA in coordination with the helicase domain [62]. The N-terminal region comprises tandem caspase activation and recruitment domains (CARDs). The RLR family includes RIG-I, melanoma differentiation-associated gene 5 (MDA5), and the laboratory of genetics and physiology 2 (LGP2), which differ in terms of their target RNA ligands (e.g., ssRNA viruses for RIG-I [63]). Upon sensing RNA viruses, DNA viruses, or bacteria-associated RNA, RIG-I is activated, and its CARD interacts with the adaptor molecule mitochondrial antiviral-signaling protein (MAVS). This interaction recruits downstream signaling molecules, such as TNF receptor-associated factor (TRAF)3/6 and members of the inhibitor of NF-κB kinase (IKK) family (IKKε, TBK1, and IKKα/β), which activate IRF-3/7 and NF-κB, leading to the production of type I/III IFNs and proinflammatory cytokines, thereby initiating an immune response [64].

It has also been shown that RLRs recognize RNA fragments from some bacteria, fungi, and parasites. During the early stages of *H. pylori* infection, RIG-I in gastric epithelial cells can recognize the 5′-pppRNA of the bacterium in a phosphorylation-dependent manner, activating downstream immune signaling pathways to secrete type I IFN and induce ISG expression to eliminate the pathogen [65]. Tatsuta et al. found that in 33 patients with active *H. pylori* infection, the antral mucosa, which was more severely affected by *H. pylori* than the gastric body, exhibited higher MDA5 expression levels, suggesting that MDA5 may be involved in the innate immune response to *H. pylori* [66]. Further analysis showed a significant association between *MDA5* mRNA expression levels and gastric mucosal atrophy and intestinal metaplasia events, suggesting that RLRs play a role in the chronicity of *H. pylori* infection, potentially as an immune evasion mechanism. In response, Xue et al. synthesized lipopeptide vaccines, Hp4 (Pam_2 Cys-modified UreB T cell epitope) and Hp10 (Pam_2 Cys-modified CagA T/B cell combined epitope), which effectively stimulated various RPPs, including RLRs, to induce maturation of bone marrow-derived dendritic cells (BMDCs) and cytokine secretion, ultimately producing a complex protective immune effect [67]. Notably, Hp10 has shown the ability to prevent *H. pylori* infection. However, *H. pylori* can evade these innate immune responses through various mechanisms, driving chronic inflammation and gastric mucosal damage that may eventually lead to cancer. Dooyema et al. found that, during infection, *H. pylori* could downregulate IRF-3 activation and induce TRIM protein expression, significantly inhibiting the STING and RIG-I signaling pathways [8]. This inhibition led to extensive neutrophil infiltration in the gastric mucosa, resulting in more pronounced acute inflammation and damage.

Kutikhin et al. comprehensively evaluated the carcinogenic potential of RLRs and CLRs, revealing that single nucleotide polymorphisms (SNPs) in the RIG-I (*RIGI*) gene might indirectly increase the risk of various neoplasias, including gastric cancer [68]. Generally, RIG-I protects against gastric cancer; *RIGI* knockdown in SGC-7901 and AGS cells significantly increased cell migration, cell viability, and the proportion of G2/M-phase cells. Correspondingly, Chen et al. found that in 90 gastric cancer patients, low RIG-I expression levels were significantly associated with advanced pathological stages and poorer prognoses, making RIG-I a potential independent prognostic indicator for patients with gastric cancer [69]. Additionally, Li et al. discovered that exosomes derived from gastric cancer cells containing THBS1 could activate the RIG-I-like signaling pathway in an m6A methylation-dependent manner, enhancing the immune function of Vγ9Vδ2 T cells by increasing cytotoxicity and promoting the production of IFN-γ, TNF-α, perforin, and granzyme B [70]. This effect was further validated using RIG-I-like receptor agonists and inhibitors, highlighting the potential for exploiting this pathway to develop gastric cancer therapies.

2.1.4 | C-Type Lectin Receptors

C-type lectin receptors (CLRs) are a type of PRR primarily expressed by APCs such as DCs, Langerhans cells, and macrophages and include secreted CLRs (e.g., the collagen lectin family) and transmembrane CLRs (further categorized into type I and type II based on their topology). These receptors monitor and respond to the extracellular milieu and endosomal compartments. A typical CLR contains one or more conserved carbohydrate-recognition domains (CRDs), which, in the presence of Ca^{2+}, bind to carbohydrates (mannose- or fucose-containing glycans) on pathogens to trigger immune responses [71].

Recent studies have shown that CLRs play a role in defending against bacterial infections, with chronic *H. pylori* infections being a significant example. DC-specific ICAM3-grabbing non-integrin (DC-SIGN), a type of CLR, primarily recognizes mannose and fucose moieties in exogenous substances and has three major functions: T cell priming, regulating DC migration, and antigen presentation. Both in vivo and in vitro studies have shown that individuals infected with *H. pylori* exhibit significantly higher levels of DC-SIGN expression compared with uninfected groups [72]. Fucose-expressing *H. pylori* can disassemble the KSRA-CNK-Raf-1 complex from the DC-SIGN signalosome, regulating IL-10 expression and suppressing IL-12 and IL-6 expression in a Raf-1-independent but LSP1-dependent manner [73]. Simultaneously, Lewis-positive *H. pylori* variants can colonize DCs by binding to DC-SIGN, resulting in downregulation of IL-6 expression [74]. Both mechanisms ultimately inhibit Th1 polarization, creating an immunosuppressive environment conducive to chronic infection. Anti-DC-SIGN, TLR2, or TLR4 antibody treatments, either alone or in combination before *H. pylori* exposure, can almost completely block IL-10 production by MDDCs [75].

In a model of chronic *H. pylori* infection, macrophage-inducible C-type lectin (Mincle) can be activated by *H. pylori* metabolites modified from host cholesterol, leading to increased IFN-γ and IL-17 production, triggering severe inflammation. In contrast, Mincle-deficient mice showed reduced histopathological severity of gastritis after *H. pylori* infection due to suppressed neutrophil and macrophage infiltration in the stomach and a decrease in the expression of proinflammatory gene sets, indicating that Mincle contributes to *H. pylori*-induced inflammation. Furthermore, *H. pylori*

not only upregulate Mincle expression but also interact with Mincle through its LPS and its released form, leading to IL-10 production and reduced pro-inflammatory cytokine levels, thereby facilitating the adaptation of *H. pylori* strains to individual hosts [76]. This mechanism may create the potential for subsequent dysplasia and carcinogenesis, although current mechanistic evidence supporting this is limited and requires further investigation.

2.2 | Gastric Epithelial Cells

The gastric epithelium is a critical barrier that separates the underlying tissues from luminal contents, forming the initial defense against external microorganisms. It consists of a continuous single layer of simple columnar epithelial cells connected by tight junction complexes [77]. The gastric epithelium's rapid regeneration and high apoptosis rate help maintain an optimal state for appropriate responses to potential threats. Additionally, the mucus coating the gastric epithelium provides lubrication, prevents microorganism colonization, and contains antimicrobial substances that can inhibit pathogen invasion and damage [78–80]. These physical and chemical barriers are generally strong enough to prevent most microorganisms from accessing the host.

H. pylori employs multiple strategies to penetrate this barrier. *H. pylori* adheres to gastric epithelial cells via specific receptors using various adhesins such as BabA, SabA, AlpA/B, HopZ, and OipA, which promote persistent colonization [81, 82]. *H. pylori* secretes enzymes like mucinase and protease, degrading the protective gastric mucus layer and allowing direct access to epithelial cells [83]. Additionally, *H. pylori* manipulates the host immune response by inducing anti-inflammatory responses and inhibiting immune cell activity, allowing it to avoid detection by the immune system and sustain chronic infection [84]. The bacteria also activate inflammatory signaling pathways in epithelial cells, inducing the secretion of pro-inflammatory cytokines such as IL-8, which attract immune cells and contribute to chronic inflammation [85].

The epithelium, however, also protects against infection and limits the damage caused by *H. pylori* to maintain tissue homeostasis. Gastric epithelial cells produce mucus, preventing direct contact and reducing bacterial adherence [86]. Tight junctions between epithelial cells maintain tissue integrity and limit the translocation of bacteria and harmful substances from the stomach lumen into underlying tissues [87]. Upon detecting *H. pylori* infection, gastric epithelial cells rapidly initiate innate immune responses, including the production of antimicrobial peptides and cytokines, which help control bacterial growth and attract immune cells to the infection site [5]. While inflammation is a critical response to *H. pylori* infection, the gastric epithelium also produces anti-inflammatory factors to mitigate excessive inflammation and tissue damage [6].

The interaction between *H. pylori* and epithelial cells involves complex signaling pathways. Through the type IV secretion system (T4SS), CagA and muropeptides are translocated into host epithelial cells, thereby activating various intracellular signaling pathways [88]. These pathways lead to increased production of pro-inflammatory cytokines and chemokines involving NF-κB, the IKK complex, JNK, p38 kinase, and AP-1 [89]. The VacA toxin binds to receptors such as RPTPα and RPTPβ, promoting ulcer formation and apoptosis through the caspase-3 pathway. It also creates channels that release cytochrome c, disrupting gastric epithelium homeostasis [90]. *H. pylori* infection also affects the cell cycle by inducing cyclin D1, promoting the proliferation of gastric epithelial cells [91]. The bacteria trigger signaling processes by binding to receptors like CD74 and MHC II molecules, leading to pro-inflammatory cytokine secretion and pro-apoptotic signal activation [92].

Persistent *H. pylori* infection significantly increases the risk of developing gastric adenocarcinoma. Chronic inflammation resulting from *H. pylori* infection results in the continuous secretion of ROS and pro-inflammatory cytokines, causing DNA damage and genomic instability in gastric epithelial cells [93]. *H. pylori*-induced inflammation also stimulates the proliferation and survival of gastric epithelial cells, increasing the chances of mutations and their accumulation. *H. pylori* infection also induces epigenetic alterations, such as DNA methylation and histone modifications, disrupting gene expression and contributing to oncogenic transformation [94]. Overall, the imbalance between cell proliferation and cell death caused by *H. pylori* infection results in the accumulation of damaged cells and potential malignant transformation [95].

Nevertheless, the gastric epithelium also protects against *H. pylori*-induced oncogenesis. It regulates the local inflammatory response initiated by *H. pylori* infection, which can cause tissue damage, by preventing the prolonged release of inflammatory mediators and ROS associated with carcinogenesis [93, 96]. The gastric epithelium possesses active DNA repair mechanisms that address the DNA damage caused by oxidative stress and inflammation, preventing the accumulation of mutations that can lead to malignant transformation [97]. Controlled cell turnover and apoptosis help to remove damaged cells, maintain epithelial integrity, and reduce the risk of cancer development [98]. Additionally, the gastric epithelium produces defensive factors, including mucins and antimicrobial peptides, limiting the impact of *H. pylori* infection by preventing direct bacterial contact and controlling bacterial growth. The production of anti-inflammatory factors helps counteract the pro-inflammatory environment induced by *H. pylori* infection, preventing conditions conducive to carcinogenesis [99].

Overall, the proper differentiation and maintenance of cellular homeostasis within the gastric epithelium are crucial for preventing cancerous changes. Healthy differentiation ensures appropriate cellular functions and reduces the likelihood of uncontrolled growth [100]. The balance between protective mechanisms and the pathogenic effects of *H. pylori* infection ultimately determines the cancer risk outcome.

2.3 | Monocytes and Macrophages

Classically, intravascular monocytes differentiate into macrophages after migrating from blood vessels into gastric tissue. Macrophages primarily function as non-selective eliminators

of exogenous pathogens and remove senescent and damaged cells. Additionally, they can process abnormal substances into small immunogenic peptides and present them to the adaptive immune system via MHC I/II molecules [101]. Furthermore, the B7 family of proteins on their surface provides secondary signals necessary for T cell activation [102].

Macrophages, predominantly the "M1" (classical and pro-inflammatory) macrophage subtype, are not solely pro-inflammatory. The "M2" (alternative and anti-inflammatory) macrophage subtype, characterized by markers such as arginase-1 and typically induced by IL-4, IL-13, IL-10, IL-1R2, and glucocorticoids, is mainly involved in anti-inflammatory processes and promoting tumor cell growth and metastasis [103]. Several studies have shown that macrophages not only facilitate a conducive environment for microbial persistence but also provide niches that allow pathogens to evade host immune responses. This is particularly crucial for certain well-known cancer-causing pathogens, such as *H. pylori* and human papillomavirus (HPV) [104–107].

The immune responses mediated by monocytes and macrophages play crucial roles in both *H. pylori* infection and gastric oncogenesis, influencing the course of these diseases. Overall, monocytes and macrophages are key components of the innate immune response to exogenous pathogens like *H. pylori*. They recognize bacterial components through PRRs and initiate the release of pro-inflammatory cytokines, such as TNF-α and IL-1β, which recruit and activate other immune cells to control the infection [108]. Macrophages can phagocytose *H. pylori* and contribute to bacterial clearance. However, *H. pylori* has developed mechanisms to evade phagocytosis and can even survive within macrophages, potentially leading to chronic infection [109].

Monocytes and macrophages may also maintain chronic inflammation in response to *H. pylori* infection. Persistent inflammation can result in tissue damage, contributing to gastritis, peptic ulcers, and gastric cancer [110]. In response to tissue damage, macrophages are involved in tissue repair and wound healing by producing growth factors and matrix remodeling enzymes. However, in chronic inflammation, these repair processes can become dysregulated, contributing to fibrosis and tissue remodeling associated with oncogenesis [111], governed by the different activation states of macrophages. In the context of *H. pylori* infection, an imbalance between M1 and M2 macrophages can impact the local immune environment and cause tissue damage [112].

In terms of gastric carcinogenesis, monocytes and macrophages can promote oncogenic signaling. Chronic inflammation induced by *H. pylori* infection can activate signaling pathways associated with cell survival and proliferation. Macrophages can secrete growth factors and cytokines that contribute to oncogenic signaling, potentially promoting the malignant transformation of epithelial cells [113]. Macrophages can also infiltrate tumor tissues and contribute to the tumor microenvironment. Tumor-associated macrophages (TAMs) have dual roles in cancers, exerting pro-tumor or antitumor functions depending on their activation state. However, TAMs generally promote angiogenesis, tissue remodeling, and immune suppression, all of which favor tumor growth and metastasis [114].

Conversely, monocytes and macrophages can protect against gastric oncogenesis. By producing anti-inflammatory cytokines such as IL-10 and TGF-β, monocytes and macrophages can modulate the immune response, reducing excessive inflammation associated with tissue damage and oncogenesis [115]. Macrophages are also involved in tissue repair and wound healing by promoting the clearance of dead cells, debris, and pathogens, preventing the accumulation of cellular debris that could contribute to inflammation and tissue damage. Proper clearance of apoptotic cells helps maintain tissue homeostasis and reduces the risk of chronic inflammation [116]. Additionally, the secretion of growth factors, such as platelet-derived growth factor (PDGF) and epidermal growth factor (EGF), can significantly promote and accelerate this process [117]. M1 macrophages, in particular, contribute to tumor surveillance by recognizing and eliminating cancerous cells, and their secreted factors promote immune activation and enhance the antitumor immune response [114].

2.4 | Neutrophils

In *H. pylori*-induced gastritis, neutrophils directly accumulate in the foveolar epithelium [118]. As a hallmark of chronic active gastritis, both peripheral and tissue-resident neutrophils outnumber macrophages early during the transition from acute to chronic inflammation [119]. This state persists in chronic inflammation, eventually damaging the mucosa. Once migrated from the circulation and activated, neutrophils further secrete chemokines such as IL-8, IL-14, IL-15, and Gro-α, transmitting danger signals to cells like T and B cells [120].

Some PRPs help neutrophils recognize *H. pylori* or its structural components, exerting direct cytotoxic effects, with *H. pylori* neutrophil-activation protein (HP-NAP) the most notable. HP-NAP is a component of *H. pylori*-derived outer membrane vesicles (OMVs) and, upon release, it continues to mediate the translocation of the apical-to-basolateral domains of epithelial cells through OMVs, interacting with gastric mucosa and immune cells, including neutrophils [121, 122]. HP-NAP acts as a chemokine for neutrophils and monocytes, directly driving neutrophils to aggregate at the site of *H. pylori* invasion in a dose-dependent manner [123]. It also promotes neutrophil transendothelial migration, induces leukocyte adhesion to vascular endothelial tissues, and facilitates extravasation, supporting the initial and rapid recruitment of neutrophils to the gastric mucosa during early *H. pylori* infection [124]. Additionally, HP-NAP upregulates the expression of β2 integrins in neutrophils and monocytes, enhancing their affinity through conformational changes, thus stabilizing adhesion to endothelial cells [125].

Furthermore, HP-NAP can directly stimulate neutrophils and monocytes to produce ROS through a ptx-sensitive GPCR, inducing oxidative stress in a dose-dependent manner [126]. Moreover, when recognized by TLR2 on neutrophils, HP-NAP promotes the synthesis and secretion of various cytokines, including IL-8, MIP-1α, and MIP-1β, and induces neutrophils to secrete myeloperoxidase to enhance degranulation [127]. These mechanisms assist in the early stages of infection by killing and controlling the invading *H. pylori*, but they also damage the gastric mucosal epithelial cells, promoting the

development and progression of gastritis [124]. Additionally, HP-NAP effectively sequesters free iron and binds DNA, protecting *H. pylori* DNA from oxidative damage. Zhao et al. showed that by simulating ROS using H_2O_2 in vitro, moderate ROS levels can upregulate SpoT expression, further increasing napA transcription by activating σ54, which promotes biofilm formation in *H. pylori* and enhances its persistence under oxidative stress [128]. Liu et al. discovered that, in both humans and mice, *H. pylori* infection reduces cathepsin C (CtsC) expression in gastric epithelial cells, induced by CagA, inhibiting NF-κB pathway activity and significantly diminishing neutrophil bactericidal capacity [129]. Behrens et al. found that exposure to *H. pylori* suppressed neutrophil expression of human CEACAM1 and CEACAM6 receptors, reducing CagA translocation efficiency and prolonging the survival of *H. pylori* within neutrophils [130]. During this period, Song et al. observed that caspase-3 activation was inhibited in neutrophils found in *H. pylori*-infected stomachs, delaying neutrophil apoptosis and inducing IL-1β secretion through autophagy independent of the NACHT/LRR/PYD domain-containing protein 3 (NLRP3)-gasdermin-D pathway [131]. These events contribute to the chronicity of *H. pylori* infection, resulting in persistent inflammation. Additionally, bacterial T4SS subunit CagL and flagellar proteins can activate the NLRP3 inflammasome, inducing IL-1β secretion and subsequent inflammatory responses. This is accompanied by major TLR2-related activation signals and bacterial protein FlaA, which facilitate bacteria-cell contact through motility [132]. Faass et al. reported that ADP-heptose metabolites, including these compounds, not only strongly activate macrophages but also significantly affect neutrophil activation [133].

2.5 | Mast Cells

Mast cells are primarily found in the skin and mucosal linings of the respiratory, genitourinary, and gastrointestinal tracts. They are best known for their participation in type I hypersensitivity reactions, but they also mediate acute inflammatory responses, tissue remodeling, angiogenesis, and wound healing [134]. During these processes, mast cells degranulate to release granules containing pre-synthesized biogenic amines, cytokines, lysosomes, and proteases. These molecules cause vasodilation and edema and also attract other inflammatory cells, like neutrophils.

Although research on the role of mast cells in the microenvironment of chronic infections and solid tumors in the stomach is relatively limited, increased numbers of mast cells have been noted in the gastric epithelium of patients suffering from *H. pylori*-induced chronic active gastritis compared with those with nonsteroidal anti-inflammatory drug (NSAID)-induced gastritis. Additionally, mast cells were found to actively participate in epithelial cell apoptosis, potentially serving as an objective indicator of gastritis activity [135]. Eissmann et al. demonstrated that IL-33 released from gastric tumor epithelium in response to IL-11 acts as an alarmin, stimulating mast cells and leading to their accumulation in the submucosa. This accumulation triggers a macrophage-associated signaling cascade, including expression of *Csf2*, *Ccl3*, and *Il6*, thereby promoting oncogenesis and disease progression [136].

2.6 | Dendritic Cells

DCs are the primary APC in the mammalian immune system, linking innate and adaptive immunity and coordinating defense against external stimuli. Compared to other well-known APCs, including macrophages and mature B cells, DCs are exceptionally efficient in activating mixed leukocytes, both in terms of quantity and activation level [137, 138]. Moreover, a unique subset of sentinel cells, plasmacytoid DCs (pDCs), can directly participate in immune responses by rapidly producing large quantities of type I interferon (IFN) [139]. While there are usually no mature DCs in healthy gastric mucosa, within the gastric tissue of individuals infected with *H. pylori*, DCs can be found in the epithelium and even extend into the lumen, playing a crucial role in the immune response to *H. pylori* infection and influencing the development of gastric cancer. The predominant DC subsets in *H. pylori*-induced gastritis are $CD11b^+CD103^-$ or $CD11c^+B220^+$, closely associated with Treg and Th17 responses [140]. Notably, *H. pylori*-activated DCs are typically less potent than those activated by other microbial pathogens, a pattern consistent with the recognition of commensal microbiota by intestinal DCs [53, 141, 142].

DCs are responsible for capturing and processing immunogenic antigens from *H. pylori* and presenting them to T cells in lymphoid tissues, thereby activating specific immune responses against the bacteria [143]. Upon activation, both human and mouse studies have demonstrated that *H. pylori*-stimulated DCs can exhibit pro-inflammatory potential, for example, by producing IL-12, driving the differentiation of Th1 cells that produce IFN-γ [144]. Hafsi et al. co-incubated *H. pylori* with human monocyte-derived DCs, observing increased MHC II and co-receptor expression and a significant increase in IL-12 production, indicating DC maturation [140]. These mature DCs promoted TNF-α and IFN-γ production in co-culture with NK cells or naïve $CD4^+$ T cells [145]. However, *H. pylori* was less effective than *Escherichia coli* in inducing these responses [146]. Additionally, studies using bone marrow-derived DCs (BMDCs) in mice demonstrated that *H. pylori* could activate DCs, inducing expression of co-receptors and the production of pro-inflammatory cytokines like IL-12, which stimulated T cell proliferation and IFN-γ production [147]. Algood et al. confirmed in *H. pylori*-infected mice that DCs migrate to the paragastric lymph nodes to elicit systemic reactions during the early stage of infection [148].

Moreover, DCs can also promote the differentiation and maturation of Tregs that suppress immune responses and induce tolerance. Although *H. pylori*-stimulated DCs express TGF-β, their levels were lower than in unstimulated DCs, potentially contributing to Treg activation [149]. However, the antigen specificity and functional capacity of these Tregs were not well examined. Evidence from DC depletion studies using CD11c-DTR transgenic mice suggested that gastric DCs play a tolerogenic role in *H. pylori* infection [150]. Depletion of $CD11c^+$ DCs increased inflammation, IFN-γ, and IL-17 production and decreased bacterial load, indicating that DCs help suppress the host immune response to *H. pylori* [151]. These studies also suggested that DCs activate Tregs, further supporting their tolerogenic function. IL-18 was important in *H. pylori*-induced tolerance, as its deficiency enhanced gastric inflammation and reduced the induction of $CD25^+$ Treg cells by

BMDCs [152]. In addition, *H. pylori*-infected mice were able to suppress allergic airway disease, highlighting the potential therapeutic applications of *H. pylori* subunits in asthma management, as they may induce immunosuppressive states [153].

Interestingly, the presence of DCs in the gastric mucosa has been correlated with the host's age; unlike in adults, only children with current *H. pylori* infection showed a marked increase in mature myeloid DCs expressing CD83 in the peripheral blood rather than in the gastric mucosa. This phenomenon may enhance tolerance to local antigens and promote chronic inflammation, partly explaining why *H. pylori* infection manifesting in childhood and frequently persists throughout life [154, 155]. Overall, gastric DCs appear to promote tolerance during *H. pylori* infection and can suppress detrimental inflammation in various disease models.

Critically, DCs can shape the immune microenvironment within the gastric mucosa. The nature of DC presentation of antigens to T cells can affect the strength and specificity of the immune response against *H. pylori*. Dysregulated or inadequate DC activation may impair immune surveillance, potentially promoting oncogenesis [156]. Furthermore, DCs contribute to immune surveillance by constantly monitoring the gastric mucosa for abnormal or infected cells. This surveillance helps identify and eliminate cells that may develop into tumors, thus preventing the progression of precancerous lesions [157]. pDCs are notably prevalent in tumor microenvironments, including gastric cancer, and they contribute to immune escape and tolerance, promoting carcinogenesis and progression [158]. Liu et al. detected a significant increase in pDCs and $ICOS^+$ Tregs in neoplastic tissue from gastric cancer patients compared with healthy controls, with levels positively associating with disease stage. $ICOS^+Foxp3^+$Tregs and pDCs in both peripheral blood and neoplastic tissues could even predict outcomes in patients with gastric cancer [159]. DCs can also promote tissue repair and healing processes by influencing the recruitment of immune cells and promoting angiogenesis [156]. This improved understanding of the protective roles of DCs has led to the exploration of DC-based immunotherapies for cancer by manipulating DCs ex vivo and reinfusing them into the body, with the aim of enhancing the immune response against tumors [160].

2.7 | Innate Lymphoid Cells

Unlike T and B cells, which primarily function in surveillance and clearance within peripheral and lymphoid tissues, most ILCs are tissue-resident and express tissue-homing receptors. ILCs are capable of self-maintenance in situ without requiring replenishment from circulating precursors [161]. A notable and essential feature of ILCs, distinguishing them from adaptive immune cells, is their capacity to generate a robust immune response to external threats without the need for APCs. This capability is particularly important in regions densely populated with commensal microbiota, such as the gastrointestinal tract, where mucosal immunity is critical [162].

2.7.1 | Group 1 ILCs

Based on their fundamental functions, group 1 ILCs (ILC1s) are classified into noncytotoxic ILC1s and cytotoxic conventional natural killer (NK) cells. Noncytotoxic ILC1s are mainly considered helper-like cells, playing a crucial role in clearing exogenous pathogens and immunosurveillance against oncogenesis. This is facilitated by their capacity to secrete cytokines and chemokines, such as IFN-γ and granzymes, upon activation by IL-15 [163]. They also express immune checkpoints and can be impaired by accumulated TGF-β in the environment [164]. However, there is still no consensus on their specific anti-tumor mechanisms, as their behaviors vary in different tumors.

NK cells are often discussed and studied separately as an indispensable subtype of ILC1s with direct cytotoxic capacity. NK cells exert potent cytotoxic effects by releasing pore-forming cytolytic molecules, such as perforin, through the death receptor pathway under the influence of TRAIL and FasL or via the antibody-dependent cellular cytotoxicity (ADCC) pathway. Additionally, NK cells secrete various cytokines and chemokines, such as TNF-α, IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF), which enhance these effects [165]. Given the unique and abundant commensal microbiota in the gastrointestinal tract, NK cells must be precisely regulated during development to dynamically adjust their activation thresholds via the expression of stimulating and suppressing receptors, thereby avoiding inappropriate or excessive immune responses [166–169]. DCs play a significant role in inducing these regulatory functions.

NK cells form the first immune barrier against *H. pylori* invasion of the gastrointestinal mucosa at an early stage. *H. pylori* can stimulate rapid proliferation and activation of NK cells, enhancing their cytotoxic effects. This response is further potentiated by the recognition of *H. pylori* antigen (HpA) via the TLR2/1 complex involving MyD88 and p38 MAPK. Concurrently, IL-12 produced by macrophages and DCs synergistically strengthens this process [145, 170–172]. In addition to their cytotoxic effects, NK cells can induce potent local inflammation by secreting IFN-γ. However, certain components of *H. pylori*, such as specific protein virulence factors and LPS, can downregulate NK cell-secreted IFN-γ, IL-2, and perforin while maintaining IL-10 production [120, 173, 174]. Moreover, interactions between *H. pylori* adhesion protein HopQ and inhibitory receptors on activated NK cells directly impair their cytotoxicity. This impairment is further exacerbated by the *H. pylori* peptide Hp(2-20), which attracts monocytes to produce lethal oxygen radicals, indirectly attenuating NK cell activity [172, 175].

The vigorous immunosurveillance and cytotoxicity of ILC1s, especially NK cells, form the foundation of their anti-tumor activity. In gastric cancer patients, ILC1s accumulate in greater numbers within neoplastic tissue than in normal background mucosa, correlating positively with patient outcomes [176, 177]. However, gastric tumor cells can modulate NK cell phenotypes by altering the expression of activating and inhibitory receptors, including NKG2D, thereby suppressing NK cell activity [178–181]. Furthermore, IFN-γ can induce the expression of the 9–27 gene in gastric tumors, reducing their susceptibility to NK cells and enhancing cancer cell migration and invasion [182]. Another classical subset of ILC1s, characterized by potent type 2 IFN production, lacks cytotoxic potential but plays a significant role in inducing Th1-axis immune responses. This subset fosters anti-tumor activity by activating cytotoxic T

lymphocytes, NK cells, and macrophages [183]. IFN-γ, produced by these cells, can upregulate MHC class I expression on cancer cells, facilitating T cell-mediated cytotoxicity, inhibiting angiogenesis, and suppressing cancer cell proliferation while inducing apoptosis [184, 185]. However, excessive secretion of IFN-γ can also promote tumor growth through persistent chronic inflammation [184]. Notably, IFN-γ can induce the expression of programmed death-ligand 1 (PD-L1) and PD-L2, leading to the immune escape of tumor cells [186–190].

2.7.2 | Group 2 ILCs

Rapid advances in molecular and cellular biology have prompted culture-independent, sequencing-based analyses that show that ILC2s are the predominant ILC subset in the stomach in both humans and mice. This predominance is mainly attributed to high expression of the IL-7 receptor protein by gastric ILC2s [7]. Unlike the relatively balanced proportions of the three distinct ILC subgroups found in the intestine, ILC2s are modulated by the transcription factors retinoic acid receptor-related orphan receptor (ROR)-α and GATA-3. These cells produce type 2 cytokines, such as IL-5, IL-9, and IL-13, and recruit and activate eosinophils, mast cells, and macrophages, thereby promoting tissue remodeling, maintaining mucosal integrity, and combating parasites [191].

Distinct from other subsets of helper-like ILCs, the immune responses orchestrated by ILC2s are highly dependent on the course of *H. pylori* infection, as observed in both patients and animal models. Initially, upon infection or tissue injury, the release of the potent alarmin IL-33 by stimulated epithelial cells and leukocytes triggers lymphocytes, especially ILC2s, to evoke acute inflammation and prime type 2 immune responses [192]. The adaptive immune response, represented by B cells, relays this protective effect through ILC2-derived IL-5 to eliminate *H. pylori* from the stomach, distinct from the Th2-dependent IgA response that occurs more frequently in the later stages [193]. As the infection persists, levels of IL-33 decline, and the role of ILC2s shifts toward promoting M2 macrophage polarization and activating STAT3, which supports tumorigenesis and progression [194]. Additionally, during the development of gastric cancer from chronic *H. pylori* infection, Li et al. observed upregulation of GATA-3 in interstitial lymphocytes, along with

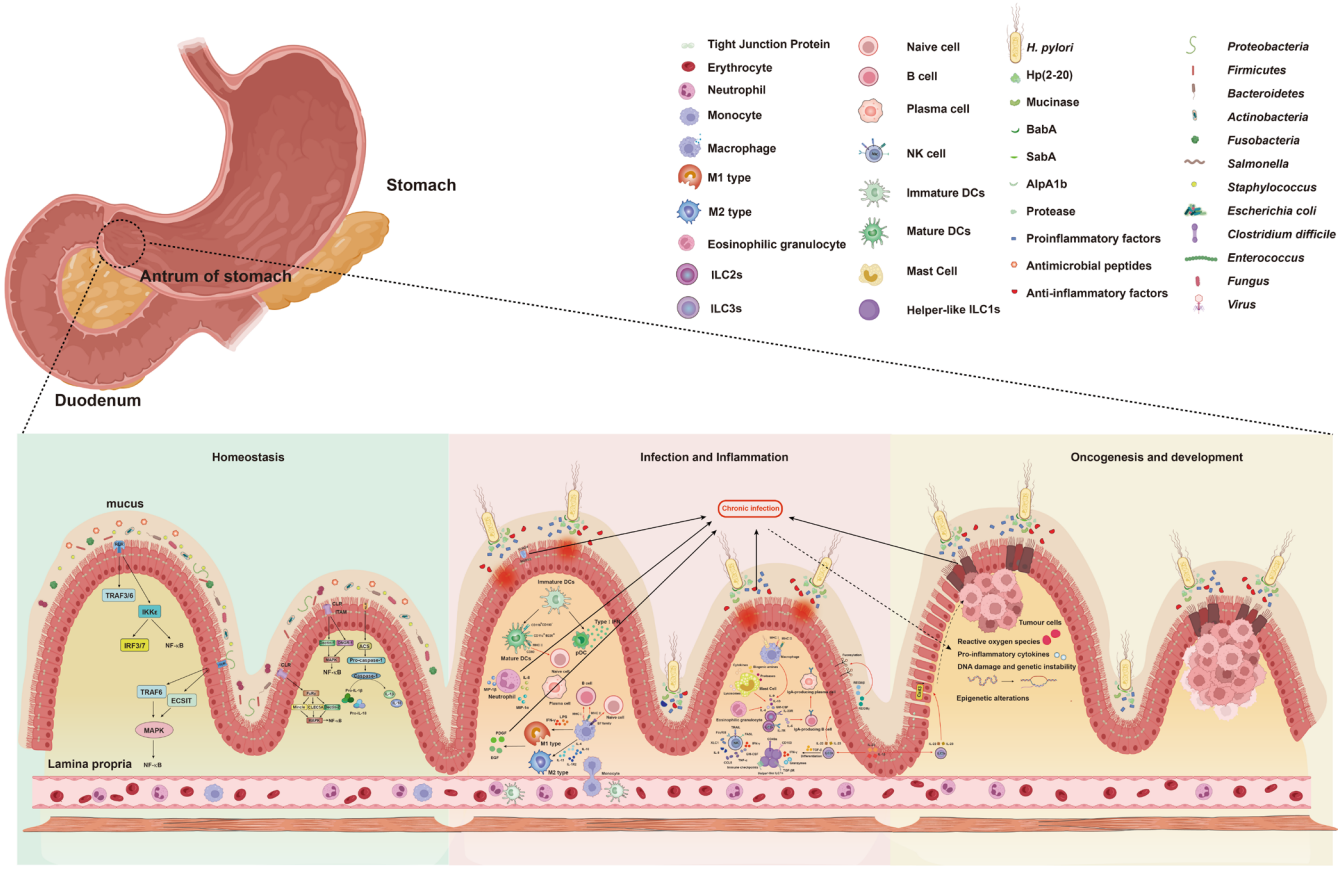

FIGURE 1 | Division and Cooperation of Different Components of Innate Immunity in Regulating Gastric Mucosa against *Helicobacter pylori* Infection and Oncogenesis. Interactions between innate immunity and *Helicobacter pylori* infection in the gastric mucosa and their relationship with gastric oncogenesis. Gastric epithelial cells maintain mucosal homeostasis (left) until challenged by *H. pylori*, which trigger robust and persistent innate responses through pattern recognition receptors, macrophages, dendritic cells, neutrophils, and innate lymphoid cells (middle). In turn, *H. pylori* subvert these responses by expressing degradative enzymes and adhesion proteins, reducing the expression of pro-inflammatory factors like IFN-γ and IL-2, inducing biofilm formation, or exploiting phagocytosis to evade immune detection. This persistent inflammatory environment creates favorable conditions for oncogenic transformation through the release of ROS, proinflammatory cytokine production, and consequent genericity. These bilateral interactions underscore the paradox of an immune system that both defends against and inadvertently promotes disease progression in response to *H. pylori*.

TABLE 1 | The roles of different innate immune cells and their cytokines in *Helicobacter pylori*-induced gastritis and oncogenesis.[a]

Cell type	Major cytokine release	Cytokine function/effects	Roles of cells in *Helicobacter pylori* infection	Roles of cells in gastric oncogenesis
Gastric epithelial cells	IL-8	Attracts activated neutrophils but also chemotactic for T cells [216]	Mucus establishes a composite protective barrier, full of antimicrobial peptides and cytokines, but can be degraded by *H. pylori* mucinase and protease [5, 83] Tight junctions prevent the translocation of bacterial and harmful substances [6] Epithelial renewal maintains mucosal structural integrity [79] Secretion of both pro- and anti-inflammatory factors for sophisticated immune responses [6, 85] *H. pylori* adhesins (BabA, SabA, and AlpA/B) promote colonization [81]	Controlling excessive inflammation with anti-inflammatory factors prevents release of ROS and inflammatory mediators and a sustained chronic status [50] Constitutive DNA repair mechanisms and controlling cell turnover and apoptosis prevent oncogene/tumor suppressor gene mutation accumulation and malignant progression [97, 98] ROS and pro-inflammatory cytokine-related DNA damage, infection-induced epigenetic alterations, and infection-associated imbalances between cell proliferation and cell death can facilitate transformation [93, 95]
Monocytes and macrophages	TNF-α, IL-1α, IL-1β, IL-6, IL-12, IL-23 IL-4, IL-10 IL-12	Characteristic "pro-inflammatory" M1 phenotype induced by *H. pylori*, chemotactic for other immune cells for pathogen elimination. via C-C motif chemokine ligand 2(CCL2), CCL3, CCL4, CCL5, CCL8, CCL11, CCL15, CCL19, and CCL20; C-X-C motif chemokine ligand 1(CXCL1), CXCL3, CXCL5, CXCL8, CXCL9, CXCL10, CXCL11, CXCL13, CXCL16 [108, 217] Maintain tissue homeostasis by limiting the inflammatory reaction and promoting tissue remodeling in response to bacterial colonization [115, 217] Rapid proliferation and activation of NK cells, enhancing their cytotoxic effects [145, 170–172]	PRRs recognize *H. pylori* structural components and initiate the release of pro-inflammatory cytokines [108] Phagocytosis contributes to bacterial clearance but can be utilized by *H. pylori* for immune evasion [109] Both dysregulated production of growth factors and matrix remodeling enzymes and an M1/M2 imbalance significantly affect the local microenvironment, impairing immunity and benefitting oncogenesis [111, 112]	Through phagocytosis and anti-inflammatory cytokine secretion, M1-type macrophages remove cell debris, reduce inflammation and chronic transformation, and monitor and eliminate cancerous cells TAMs can promote angiogenesis, tissue remodeling, and immune suppression [114, 116] Factors like PDGF and EGF stimulate tissue regeneration and healing to promote malignant transformation of epithelial cells [117]

(Continues)

TABLE 1 | (Continued)

Cell type	Major cytokine release	Cytokine function/effects	Roles of cells in *Helicobacter pylori* infection	Roles of cells in gastric oncogenesis
Neutrophils	IL-8, IL-14, IL-15, Gro-α MIP-1α, MIP-1β	Transmitting danger signals to T and B cells, which are subsequently activated [120] Promote secretion myeloperoxidase to enhance degranulation and promote bacterial killing [127]	Gastric epithelial cells orchestrate neutrophil recruitment and aggregation to eliminate *H. pylori*, although this can lead to unwanted tissue damage in the acute phase [120]	Neutrophils produce reactive oxygen metabolites and neutrophilic proteases, which mediate tissue damage and potential accumulation of DNA damage [216]
Dendritic cells	IL-6, IL-8 IL-12 IFN-γ, IL-17, IL-18	Trigger T cell IFN-γ secretion to drive Th1 response to eliminate bacteria [139, 218] Drives DC maturation and differentiation of Th1 cells that produce pro-inflammatory IFN-γ to eliminate bacteria Rapid proliferation and activation of NK cells, enhancing their cytotoxic effects [144, 145, 170–172] Activate Tregs to limit host immune response [151, 152]	DCs process constitutive elements of *H. pylori* and present antigens to T cells to initiate specific defense responses; meanwhile, DC-derived IL-12 drives differentiation of Th1 cells to control intracellular infection [143, 144] DCs are involved in promoting tissue repair, healing, and restoring tissue homeostasis in several ways, such as promoting Treg differentiation [149]	Exert crucial capacity of immune surveillance and preventing precancerous lesion progression [157] Reinfusing manipulated DCs ex vivo can enhance the host's anti-tumor immune effects [160]
Group 1 innate lymphoid cell	IFN-γ, GM-CSF, granzymes	Pro-inflammatory response and cytotoxicity via Th1 T cell effector responses [145, 163, 165]	NK cell-secreted IFN-γ effectively triggers local inflammation [165] *H. pylori* not only stimulate rapid NK proliferation and activation to augment their cytotoxicity, which can be impaired by both HopQ and Hp(2-20), but can also downregulate NK cell-derived IFN-γ, IL-2, and perforin [120, 170–175]	NK cells exert vigorous immunosurveillance and cytotoxicity against tumor cells Tumor cells suppress their phenotype by modulating the balance between activating and inhibitory receptors [179, 180] Noncytotoxic ILC1s mainly participate in Th1-axis immune responses for their anti-tumor function [183] IFN-γ not only upregulates MHC I expression by tumor cells to suppress their growth, but also benefits tumor growth through persistent chronic inflammation and induction of 9–27 genes in gastric cancers that reduce susceptibility to NK cells, enhance migration and invasion, and increase PD-L1 and PD-L2 expression for immune escape [182, 184–190]

(Continues)

TABLE 1 | (Continued)

Cell type	Major cytokine release	Cytokine function/effects	Roles of cells in *Helicobacter pylori* infection	Roles of cells in gastric oncogenesis
Group 2 innate lymphoid cell	IL-5, IL-9, and IL-13 IL-5	Recruit and activate eosinophils, mast cells, and macrophages, thereby promoting tissue remodeling, maintaining mucosal integrity [38] Promotes differentiation of IgA-producing B cells into IgA-producing plasma cells to eliminate *H. pylori* [219]	ILC2-related immune responses feature in an infective course-dependent manner Initially, IL-33 stimulated-ILC2s evoke acute inflammation and prime for type 2 immune responses; later, they promote M2-type macrophage polarization and activate STAT3 [194, 195] ILC2-derived IL-5 provides fuel for the protective effect of adaptive immunity to eliminate *H. pylori* [193]	ILC2s upregulate GATA-3 expression to decrease Connexin-43 at gastric epithelial gap junctions, promoting oncogenesis Produce amphiregulin for further tissue invasion and metastasis CXCL12/CXCR4 signaling benefits pre-metastatic niche development [196, 200, 204–206] Both depleting ILC2s and blocking related signaling pathways prevent tumor development and reverse pathological alterations [208, 209]
Group 3 innate lymphoid cell	N.A.	N.A.	N.A.	IL-17 and IL-22 secreted from ILC3s mediate pro-tumorigenic STAT3 activation and ILC3/IL-22 shuttling [220, 221]

Abbreviation: N.A., not applicable.
[a]Indirect evidence is not presented here.

enhanced populations of $Lin^{-}GATA\text{-}3^{+}$ and $Lin^{+}GATA\text{-}3^{+}$ cells, highlighting the pivotal role of ILC2s [195].

In contrast to the complex effects of ILC1s, ILC2s primarily contribute to promoting tumorigenesis and immune suppression. There is a notable increase in the frequency of ILC2s in the peripheral blood of gastric cancer patients compared with healthy individuals [196]. This is thought to be due to a Th1/Th2 imbalance and upregulation of myeloid-derived suppressor cells (MDSCs) and M2 macrophages, which play significant immunosuppressive roles in the tumor microenvironment [196–198]. Furthermore, the expression of Connexin-43 (Cx43), a significant component of gap junctions in normal gastric mucosa, is decreased by higher expression of GATA-3 associated with ILC2s, contributing to the development of gastric cancer [199]. In a mouse model of gastric cancer, there was expansion of $CXCL12^{+}$ endothelial cells and $CXCR4^{+}$ ILC2s, coinciding with an abnormal proliferative tendency of isthmus stem cells. The high expression level of Wnt5a in ILC2s and RhoA signaling activation played crucial roles in this process [200–202]. The CXCL12/CXCR4 signaling pathway also facilitates the development of a pre-metastatic niche, creating a more favorable environment for tumor cells to enter systemic circulation [203–205]. Additionally, ILC2-secreted amphiregulin has been found to promote malignant behaviors, such as tissue invasion and metastasis, in EGFR-expressing tumors, including gastric cancer [206]. Several studies have confirmed that therapies targeting ILC2s by depleting them or blocking ILC2-related signaling pathways effectively prevent cancer development and even reverse pathological changes associated with metaplasia [207, 208].

2.7.3 | Group 3 ILCs

While ILC3s exert significant immune functions in the intestinal mucosa, they are almost absent in the stomach. ILC3s, characterized by the expression of RORγt and aryl hydrocarbon receptor (AHR), similar to Th17 cells, primarily maintain intestinal homeostasis by producing IL-22. This cytokine regulates the secretion of antimicrobial peptides, including regenerating islet-derived (REG) IIIβ and IIIγ, and promotes the fucosylation of gastric epithelial cells. Additionally, IL-33 secreted by ILC3s can activate ILC2s [162, 165, 209, 210]. Some ILC3s can also express MHC to present antigens to $CD4^{+}$ T cells, eliciting tumor-related adaptive immune responses [164, 211, 212]. Furthermore, under the influence of TGF-β, ILC3s can convert into regulatory ILCs or ILC1s, leading to a significant reduction in pro-inflammatory capacity and anti-tumor effects [178].

However, the exact functions and status of ILC3s in the stomach are not yet fully understood. In intestinal cancer, ILC3s have been implicated in processes that promote tumor growth and metastasis, as also reported in a few studies on pancreatic cancer and hepatocellular carcinoma [213, 214]. Fu et al. collected peripheral blood samples from 62 patients with gastritis, premalignant lesions, and various stages of gastric cancer, finding elevated levels of ILC3s and IL-22 compared with healthy controls [215]. Nevertheless, further research is necessary to fully elucidate the complex immune functions of ILCs in the context of gastric cancer.

3 | Conclusion and Outlook

In summary, understanding the complex role of innate immunity in *H. pylori* infection and its contribution to gastric oncogenesis could pave the way for new preventative and anti-tumor strategies. *H. pylori* triggers robust innate responses through pattern recognition receptors, macrophages, dendritic cells, neutrophils, and innate lymphoid cells (Figure 1). There are numerous bidirectional interactions between *H. pylori* and the various cells of the host innate immune cells and their molecular products. Monocytes and macrophages, and ILCs detect *H. pylori* to clear the pathogen through pro-inflammatory cytokine release, phagocytosis, further recruitment and differentiation of innate inflammatory cells, and local inflammation. DCs also prime the immune system for adaptive immunity. Conversely, *H. pylori* subverts these responses by expressing degradative enzymes and adhesion proteins, reducing the expression of pro-inflammatory factors like IFN-γ and IL-2, inducing biofilm formation, or exploiting phagocytosis to evade immune detection.

Thus, the bilateral interactions could also allow the pathogen to evade immune defenses and establish chronic infection, which, over time, leads to sustained inflammation, tissue remodeling, and immune dysregulation within the gastric mucosa, as outlined in Table 1. This persistent inflammatory environment creates favorable conditions for oncogenic transformation, underscoring the paradox of an immune system that both defends against and inadvertently promotes disease progression in response to *H. pylori*.

As antibiotic resistance complicates current *H. pylori* eradication strategies, this review highlights the potential of immunomodulatory approaches that could enhance the antimicrobial effect of existing or new agents while mitigating chronic inflammation when maintaining pathogen control. Targeting specific elements of the immune response may provide new avenues for simultaneously enhancing antimicrobial efficacy while reducing gastric cancer risk in individuals with chronic *H. pylori* infection. Furthermore, understanding how the innate immune system influences cancer development and progression could provide new targets for the treatment of early, dysplastic lesions or even established invasive cancer.

Author Contributions

Yuheng Zhang and **Zhiyu Yan:** conceptualization. **Yuheng Zhang**, **Zhiyu Yan**, and **Yuhao Jiao:** data acquisition. **Yuheng Zhang** and **Zhiyu Yan:** writing – original draft preparation. **Yunlu Feng** and **Shengyu Zhang:** writing – review and editing. **Yuheng Zhang**, **Zhiyu Yan**, and **Yuhao Jiao:** visualization. **Aiming Yang:** supervision. All authors have read and agreed to the published version of the manuscript.

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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