Effects of *Helicobacter pylori* on tumor microenvironment and immunotherapy responses

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**INTRODUCTION**

*Helicobacter pylori* is a gram-negative, helical, microaerophilic, and flagellated bacteria that colonizes the gastric mucosa in approximately 50% of the world population (1, 2). *Helicobacter pylori* infection is the main cause of gastric mucosal diseases such as gastric cancer (GC), chronic non-atrophic gastritis, atrophic gastritis, intestinal metaplasia, and dysplasia (3). GC is the fifth most common cancer and the fourth leading cause of cancer-related deaths worldwide (4). *H. pylori* is classified by the WHO as a class I carcinogen associated with the onset of GC, as chronic *H. pylori* infection leads to at least 75% of GC cases (5–8). 2% of *H. pylori* infected patients will develop GC (7).

Tumor growth is supported by oncogene-driven metabolic activities as well as by the microenvironment. Infection with *H. pylori* promotes gastric tumorigenesis, mainly by influencing the microenvironment (9). Virulence factors such as cytoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), urease (Ure), arginase (Arg),
lipopolysaccharide (LPS), and neutrophil-activating protein (NAP), enable *H. pylori* to survive and colonize the gastric mucosa, maintain chronic inflammation, and induce malignant changes within the gastric mucosa (1, 10–12). The immune system plays a pivotal role in eliminating *H. pylori* infection and controlling inflammation. Throughout a long-term co-existence with human hosts, *H. pylori* has developed several strategies to maintain a balance between the immune response and immune escape (13, 14). Through regulating tumor stromal cells, immune checkpoints, and other regulatory factors, *H. pylori* constructs a microenvironment that favors persistent colonization and facilitates tumorogenesis.

However, the influence of *H. pylori* on responses to immunotherapies and the prognosis of GC remains controversial (15–18). Recent studies have presented that *H. pylori* infection might affect the curative effect of tumor therapy by the induced immuno-regulation (19, 20). Besides, *H. pylori* virulence factors such as NAP, VacA, and Ure might elicit or enhance immune responses, which indicates the potential application in vaccine development and tumor immunotherapy (21, 22). These virulence factors are immunodominant antigens of *H. pylori* and might improve patient prognosis as immunogens or adjuvants in immunotherapy (23). Here, this review describes the mechanisms and effects of *H. pylori* on the immune microenvironment of GC and tumor immunotherapy responses.

### Effects of *H. pylori* on tumor stromal cells in gastric tumor immune microenvironment

The tumor microenvironment (TME) consists of a continuously evolving complex of tumor cells and stroma. Stroma comprises surrounding non-cancerous fibroblasts, epithelial, immune and blood cells, and extracellular components such as cytokines, growth factors, hormones, and extracellular matrix (ECM) (24, 25). Stroma plays a key role during tumor initiation, progression, and metastasis, meanwhile it significantly influences therapeutic responses and clinical outcomes (26). *Helicobacter pylori* and its virulence factors can form a microenvironment that facilitates its survival and colony formation by regulating the constituents and functions of the TME. This section summarizes the interactions between *H. pylori* and tumor stromal cells during GC initiation, progression, and metastasis and describes potential strategies to improve the prognosis (Figure 1; Table 1).

### Effects of *H. pylori* on tumor-associated macrophages in gastric tumor immune microenvironment

Changes in immune responses and the immune escape of *H. pylori* are closely associated with tumor-associated macrophages (TAMs), which are emerging key players in the TME. Macrophages play crucial roles in host defense against bacterial infections and in the regulation of immune responses during *H. pylori* infection (68). However, macrophages can also induce angiogenesis and suppress the host immune response during cancer development (37, 69). Generally, TAMs comprise M1 and M2 subtypes (27). Proinflammatory activated M1 macrophages promote the type I T helper (Th1) immune response by producing type I proinflammatory cytokines such as IL-1β, IL-1α, and IL-6 to clear pathogens and inhibit tumor progression, while simultaneously suppressing Th2-type responses (27, 70, 71). Activated M2 macrophages contribute to production of ECM and anti-inflammatory effectors such as IL-4 and IL-10 that are involved in the Th2 immune response, promotion of wound healing, and suppression of Th1 responses (72–75). Additionally, a third type called regulatory macrophages (Mregs) secretes abundant IL-10 that limits inflammation but do not secrete ECM (72). *Helicobacter pylori* and other pathogens might impair M1 macrophage differentiation while inducing M2 macrophage differentiation or M1 transdifferentiation into M2 macrophages, which can promote tumor progression and invasion by inducing angiogenesis and mediating immunosuppressive signals in solid tumors (27).

Furthermore, *H. pylori* infection might regulate specific microRNAs (miRNAs) to control macrophage function and affect the TME (28, 76). Infection with *H. pylori* leads to the downregulated expression of miR-4270 by human monocyte-derived macrophages. This favors upregulation of expression of CD300E immune receptors that enhance the proinflammatory potential of macrophages. However, the expression and exposure of major histocompatibility complex class II (MHC-II) molecules on the plasma membrane are simultaneously compromised. Hence, antigen presentation ability is decreased, leading to persistent *H. pylori* infection (28). The upregulation of let-7i-5p, miR-146b-5p and miR-185-5p, and miR146b expression in macrophages caused by *H. pylori* infection can similarly decrease HLA-II expression on the plasma membrane, which ultimately compromises bacterial antigen presentation to Th lymphocytes and impairs immune responses against *H. pylori* (29, 30). Collectively, *H. pylori* infection mainly downregulates surface recognition factors at the transcriptional level by rendering macrophages fail to degrade the bacteria. Thus, macrophages become a protective niche for *H. pylori*.

*Helicobacter pylori* can induce the production of specific enzymes that regulate macrophage function and affect TME. The production of arginase II (Arg2) in macrophages induced by *H. pylori* infection results in cell apoptosis and restrained proinflammatory cytokine responses, thus promotes *H. pylori* immune evasion (31, 32). Matrix metalloproteinase 7 (MMP7) plays a pivotal role in *H. pylori*-mediated immune escape (33). Heme oxygenase-1 (HO-1) expression in macrophages also be induced, resulting in a polarization switch towards a reduction
in the M1 population and an increase in the Mreg profile, causing innate and adaptive immune responses failure (34). Transfer exosomes expressing mesenchymal–epithelial transition (MET) factor, a cell-surface receptor tyrosine kinase from *H. pylori*-infected GC cells, can elicit uncontrolled macrophage activation and downstream inflammation and might be associated with tumorigenesis and cancer development (35). These findings shed light on how *H. pylori* influences the gastric microenvironment by inducing the expression of macrophage-associated enzymes in TAMs.

Moreover, *H. pylori* upregulates the expression of Jagged 1, a ligand of Notch signaling that plays an important role in M1 macrophage activation and bactericidal activity to prevent *H. pylori* infection. Upregulated Jagged 1 expression induces an increase in the expression of proinflammatory mediators and phagocytosis and a decrease in the bacterial load, which together impart antibacterial activity in macrophages (36). The hedgehog (HH) signaling pathway also plays an important role in the gastric TME. Sonic hedgehog (SHH) induced by *H. pylori* infection acts as a macrophage chemoattractant, which is a prerequisite in the gastric immune response (37).

In conclusion, *H. pylori* infection at the early stage can induce the infiltration of polymorphonuclear leukocytes and mononuclear phagocytes in the gastric mucosa as an innate immune response (77). During the advanced stages of GC, *H. pylori* can escape immune surveillance by impairing the antigen presentation of TAMs or by disrupting the M1/M2 (or Mreg) balance in favor of an M2 (or Mreg) phenotype (34, 72). Immunosuppressive status eventually promotes tumorigenesis and cancer development (78). These mechanisms also provide the potential for investigating novel targeted drugs (79). Specific miRNAs such as let-7i-5p, miR-146b-5p, and miR-185-5p can be targeted to reduce adverse effects on macrophage antigen presentation (29). Targeting specific enzymes including MMP7 and HO-1 or signaling pathways, such as Notch and HH, to regulate the M1/M2 (or Mreg) balance might also warrant investigation (33, 34).
| Tumor cells affected by *H. pylori* | Roles of *H. pylori* | Results |
|-----------------------------------|----------------------|---------|
| **TAMs** | Simultaneous impairment and induction of M1 macrophage and M2 macrophage differentiation, respectively, or transdifferentiation to M2 macrophages (27) | Promotes tumor progression and invasion by inducing angiogenesis and mediating immunosuppressive signals in solid tumors |
| Regulation of specific miRNAs | Downregulates miR-4270 expression (28) | Impairs MHC-II expression and exposure, decreases antigen presentation ability, favors persistent *H. pylori* infection |
| | Uregulates let-7i-5p, miR-146b-5p, miR-185-5p, and miR146b expression (29, 30) | Inhibits HLA-II expression, compromises bacterial antigen presentation to Th lymphocytes, impairs immune responses to *H. pylori* |
| **Induces production of specific enzymes** | Arg2 (31, 32) | Promotes immune escape of *H. pylori*, mediates macrophage apoptosis, restraints inflammatory responses |
| **Regulation of some signaling pathway molecules** | Uregulation of Jagged 1 expression (36) | Increases secretion of proinflammatory mediators and phagocytosis, decreases bacterial load, confers anti-bacterial activity on macrophages |
| **MSCs** | Upregulates CXCR4 expression and enhances MSCs migration toward SDF-1 (38) | Enhances BM-MSC migration into gastric tissues |
| | Recruits or induces BM-MSCs and hA-MSCs | Promotes *H. pylori*-mediated gastric tumorigenesis and development |
| **Induces MSC differentiation into CAFs** | Alters THBS expression (45, 46) | Promotes survival, proliferation, and migration of GC cell lines, inhibits antitumor functions of T cells in GC TME |
| **Stimulates BM-MSC differentiation into CAF myofibroblasts** | Increases HDGF expression (49) | Enhances tumor cell ability to proliferate, invade, and metastasize (49, 50) |
| **Induces fibroblast transdifferentiation into myofibroblasts** | Upregulates and downregulates HIF-1α and Bax expression, respectively (51) | Promotes gastric tumorigenesis |
| **Propels EMT via signal pathways and TGF-β secretion** | Induces activation or differentiation of rat gastric fibroblasts by NF-κB and STAT3 signaling (52) | Promotes Snail1 expression and propels EMT leading to GC progression |
| | Secretes TGFβ1 and regulates TGFβR1/R2-dependent signaling in *H. pylori*-activated gastric fibroblasts (53–55) | Prompts reprogramming normal gastric epithelial cells towards a precancerous phenotype and promotes EMT in normal epithelial cells |
| **Induces differentiation of SLFN4+ MDSCs** | HH/Gli1 (56, 57) | Inhibits gastric inflammatory response by *H. pylori*, suppresses T cell function, immune dysregulation, and tumor progression |
| **Interaction between *H. pylori* and MDSCs is regulated by several factors** | miR130b (59) | Activates SLFN4+ MDSCs and promotes *H. pylori*-induced metaplasia |
| | ASK1 (25, 60) | Suppresses inflammation induced by infiltrating immature MDSCs |
| | IL-22 (61) | Induces expression of proinflammatory proteins, suppresses Th1 cell responses, promotes development of *H. pylori*-associated gastritis |
| | PD-L1 (62–64) | Promotes tumor infiltration of MDSCs, mediates resistance to anti-PD-1/PD-L1 therapy |

(Continued)
**Effects of *H. pylori* on recruiting and inducing bone marrow-derived mesenchymal stem cells in gastric tumor immune microenvironment**

Multipotent mesenchymal stem cells (MSCs) can self-renew and differentiate into various cell types that play key roles in tissue healing, regeneration, and immune regulation (80). Bone marrow-derived mesenchymal stem cells (BM-MSCs) might play important roles in *H. pylori*-associated gastric tumorigenesis and immunosuppression. Upon sensing signals indicating gastric mucosa damage, BM-MSCs migrate from bone marrow to stomach via the peripheral circulation. BM-MSCs heal damaged mucosa through a paracrine mechanism. BM-MSCs also participate in gastric tumorigenesis by increasing cancer-associated fibroblasts (CAFs) (39, 41). Human adipose-derived mesenchymal stem cells (hAD-MSCs) also participate in gastric tumorigenesis by increasing tumor cells invasion and metastasis during *H. pylori* infection (42).

In addition to malignant transformation, MSCs can promote tumorigenesis locally and systemically by compromising cancer immune surveillance or altering tumor stroma. When transplanting BM-MSCs in *H. pylori* infected mice model, IL-10 and transforming growth factor-β1 (TGF-β1) can be increased, as well as T cells secreting IL-10 and CD4+ CD25+ Foxp3+ regulatory T (Treg) cells in splenic mononuclear cells (43, 44). BM-MSCs can reduce the fraction of T cells that produce IFN-γ, thus inhibiting CD4+ and CD8+ T cell proliferation. Local and systemic immunosuppression mediated by BM-MSCs contributes to GC development induced by *H. pylori* (43).

MSCs can also promote tumorigenesis by altering tumor stromal components. Thrombospondin (THBS) promotes tumorigenesis through crosstalk with BM-MSCs. Infection with *H. pylori* significantly upregulates the expression of THBS4 in BM-MSCs. Overexpressed THBS4 then mediates BM-MSC-induced angiogenesis in GC by activating the THBS4/integrin α2/PI3K/AKT pathway (45). Moreover, BM-MSCs can differentiate into pan-cytokeratin-positive (pan-CK+) epithelial cells and alpha-smooth muscle actin (α-SMA+) cancer-associated fibroblasts (CAFs) by secreting THBS2, thus promoting the development of *H. pylori*-associated GC (46).

BM-MSCs play pivotal roles in *H. pylori*-associated GC. The immune regulatory functions of MSCs remain obscure. Shedding light on these functions and their mechanisms will provide clues on therapeutic targets for preventing GC development.

**Effects of *H. pylori* on induction of cancer-associated fibroblasts in gastric tumor immune microenvironment**

CAFs are activated myofibroblasts that accompany solid tumors and are principal constituents of tumor stroma (84, 85). They play important roles in the TME. They can create a niche for cancer cells and promote cancer progression by stimulating cancer cell proliferation, migration, invasion, and angiogenesis (85–87). Proinflammatory and tumor-associated factors secreted by CAFs might induce persistent inflammation or intervene in tumor immunity, thus mediate tumor immune escape (52, 88). Mainly derived from MSCs, CAFs could induce epithelial-mesenchymal transition (EMT), which enhances the invasive properties of malignant cells (89, 90) that detach from primary tumor site to surrounding tissues (91).

Helicobacter pylori infection can induce MSCs differentiating into CAFs, and upregulate the expression of fibroblast markers, fibroblast activation protein (FAP), CAF activation markers, and aggressive/invasive markers (47). FAP-positive CAFs enhance the survival, proliferation, and migration of GC cell lines and inhibit T cells function (48). *H. pylori* infection also increases the

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**TABLE 1 Continued**

| Tumor cells affected by *H. pylori* | Roles of *H. pylori* | Results |
|-----------------------------------|----------------------|---------|
| BM-MSCs | KLF-4 (65–67) | Promotes recruitment of MDSCs to tumors, creates immunosuppressive microenvironment, promotes tumor growth |
expression of hepatoma-derived growth factor (HDGF) (49, 50). Exposure to HDGF promotes the recruitment of BM-MSCs, stimulates their differentiation into CAF-myofibroblasts, and enhances tumor cell proliferation, invasiveness, and metastasis (49). Moreover, H. pylori infection can induce fibroblasts transdifferntiating into myofibroblasts, which upregulating the early carcinogenic marker hypoxia-inducible factor 1-alpha (HIF-1α) and downregulating proapoptotic bcl-2-like protein 4 (Bax) expression (51).

CAFs induced by H. pylori propel EMT by nuclear factor kappa B (NF-κB), signal transducer and activator of transcription 3 (STAT3), and TGF-β. Helicobacter pylori might induce the activation or differentiation of rat gastric fibroblasts in vitro, which then activate NF-κB and STAT3 signaling, and upregulate Snail1. This is an EMT-inducing transcription factor (EMT-TF) (52). As a major propeller of EMT in cancer progression and metastasis (53, 54), TGF-β can initiate tumorigenesis by activating EMT-type III initiation in epithelial cell compartments at the early stage of cancer development (55, 92). Gastric fibroblasts activated by H. pylori promote normal gastric epithelial cells to precancerous phenotype, and promote EMT by regulating TGFβ1/R2-dependent signaling (55). The HH, Wnt, and Notch signaling pathways can interact with TGF-β pathway and induce EMT progression (93–97).

Collectively, persistent H. pylori infection increases the differentiation of CAFs, which propel EMT through NF-κB, STAT3, and TGF-β. As CAFs play key roles in the gastric microenvironment, targeting CAFs might be a potential strategy to improve the prognosis of patients (98, 99).

Effects of H. pylori on myeloid-derived suppressor cells in gastric tumor immune microenvironment

Immature myeloid (progenitor) cells (IMCs) do not mediate immunosuppression in healthy individuals. However, chronic inflammation, infections, and autoimmune diseases impair IMC differentiation and decrease peripheral myeloid cells numbers, resulting in more myelopoiesis (100–103). This eventually results in myeloid-derived suppressor cells (MDSCs) accumulation and immunosuppression (102, 104). MDSCs mediate immune suppression by inducing immunosuppressive cells (105), blocking lymphocyte homing (106), producing reactive oxygen and nitrogen species (107, 108), exhausting critical metabolites for T cell function (109), expressing negative immune checkpoint molecules (110).

Interactions between H. pylori and MDSCs are important in gastric immune microenvironment. On one hand, H. pylori can induce the differentiation of myeloid cell differentiation factor Schlafen 4 (SLFN4+) MDSCs (56, 58). This factor marks a subset of MDSCs in the stomach during H. pylori-induced spasmyotic polypeptide-expressing metaplasia (SPEM) (57). During chronic H. pylori infection in mice model, a subset of HH-Gi1-dependent immune cells is recruited to the gastric epithelium, and polarizes into SLFN4+ MDSCs. Overexpression of the SHH ligand in infected WT mice accelerates SLFN4+ MDSCs differentiation in gastric corpus (57). Furthermore, H. pylori can stimulate plasmacytoid dendritic cells to secrete IFN-α through toll-like receptor 9-myeloid differentiation factor 88-interferon regulatory factor 7 (TLR9-MyD88-IRF7 pathway) (58).

Differentiated SLFN4+ MDSCs inhibit gastric inflammatory response induced by H. pylori and suppress T cell function (56–59). Persistent immune dysregulation then favors intestinal metaplasia and neoplastic transformation, which leads to immune disorders and tumor progression.

Several markers, such as MiR130b, apoptosis signal-regulating kinase 1 (ASK1), interleukin 22 (IL-22), programmed death-ligand 1 (PD-L1), and Krüppel-like factor 4 (KLF4) play regulatory roles in the interactions between H. pylori and MDSCs. MiR130b produced by SLFN4+ MDSCs suppress T cells function and promote H. pylori-induced metaplasia (59). ASK1 deficiency promotes a Th1-dependent immune response and recruits immature Gr-1+Cd11b+ MDSCs with H. pylori infection. This could lead to the development of gastric atrophy and metaplasia (25, 60). Moreover, IL-22 secreted by polarized Th22 cells induced by H. pylori can stimulate CXCL2 production from gastric epithelial cells. This causes CXCR2+ MDSCs migration to gastric mucosa, where they produce proinflammatory proteins and suppress Th1 cell responses, contributing to the development of H. pylori-associated gastritis (61). PD-L1 upregulation on the surface of gastric epithelial cells at the early stage of H. pylori infection (62) promotes tumor infiltration of MDSCs (63) and then lead to anti-PD-1/PD-L1 treatment resistance (64). KLF4 is an evolutionarily conserved zinc finger transcription factor and key regulator of diverse cellular processes (111–113).

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Effects of *H. pylori* on PD-1/PD-L1 in gastric tumor immune microenvironment

In addition to cells in TME, immune checkpoints are involved in regulating *H. pylori*-associated TME. (Table 2).

The 55 kDa transmembrane protein programmed death 1 (PD-1) is expressed in activated T cells, natural killer (NK) cells, B lymphocytes, macrophages, dendritic cells (DCs), and monocytes. It is abundantly expressed in tumor-specific T cells (126–128). PD-L1 (also known as CD274 or B7-H1) is a 33 kDa type I transmembrane glycoprotein that is widely expressed in macrophages, activated T lymphocytes, B cells, DCs, and also expressed in tumor cells (129). Binding of PD-1 and PD-L1 enhances T cell tolerance, inhibits T cell activation and proliferation, increases Th cell transformation to Foxp3+ Treg cell, and prevents T cell cytolysis in tumor cells (130). Thus, interaction between PD-1 and PD-L1 is a double-edged sword. It can inhibit immune responses and promote self-tolerance, while it can also lead to immune escape and tumor progression.

*Helicobacter pylori* infection could upregulate PD-1/PD-L1 expression in gastric ulcers and GC patients (119), which might be related with poor prognosis (131, 132). Chronic *H. pylori* infection could cause excessive damage to gastric mucosa. Upregulated PD-1/PD-L1 is launched to avoid such damage, meanwhile this also reduces T cell-mediated cytotoxicity and promotes GC progression (119–121). SHH pathway is involved in PD-L1 upregulating (62). As an HH transcriptional effector, zinc finger protein GL1, mediates mammalian target of rapamycin (mTOR)-induced PD-L1 expression in GC organoids (64). Kinds of *H. pylori* virulence factors are reported in this process. *H. pylori* T4SS components activate p38 MAPK pathway and upregulate PD-L1 expression, thus inhibiting T cell proliferation and inducing Treg differentiation from naive T cells, which lead to immune escape (122, 123).

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**Effects of *H. pylori* on tumor immunotherapy responses**

Immunotherapy stimulates the immune system against neoplasms and harnesses the specificity of innate immune to fight cancer, particularly by activating T-cell mediated immunity (137, 138). With the wide application of immune therapy, the immune checkpoint inhibitors (ICIs) targeting immune checkpoint molecules such as PD-1 and CTLA-4, and other immune therapies such as cancer vaccine, the immune cells input, antigen vaccine, oncolytic viruses, and recombinant cytokines, have been receiving worldwide attention and have made a certain progress (139–147). However, as lack of optimal criteria selecting suitable patients until now, the objective response rate of immunotherapy remains low (148, 149). Hence, factors that influence the effectiveness of tumor immunotherapy need to be identified. In this section, we focused on the effects and potential applications of *H. pylori* infection on tumor immunotherapies (Figure 2; Table 3).

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**TABLE 2 Effects of *H. pylori* on tumor-related proteins in gastric tumor immune microenvironment.**

| Tumor-related proteins affected by *H. pylori* | Roles of *H. pylori* | Results |
|----------------------------------------------|----------------------|---------|
| PD-1/PD-L1                                   | Upregulates PD-1/PD-L1 expression (119–121) | Reduces excessive damage induced by *H. pylori*, reduces T cell-mediated cytotoxicity, promotes GC progression |
|                                              | Upregulates PD-L1 expression by *H. pylori* CagA through the SHH pathway (62) | Inhibits T cell proliferation and Treg cell induction from naive T cells, increases immune escape, promotes GC progression |
|                                              | Upregulates PD-L1 expression by mTOR-GLI signaling (64) | |
|                                              | Upregulates PD-L1 expression by the p38 MAPK pathway (122, 123) | |
|                                              | Upregulates PD-L1 expression by *H. pylori* urease subunit through the Myh9/mTORC1 pathway (124) | |
|                                              | Upregulates PD-L1 expression by *H. pylori* LPS through the NF-kB pathway (125) | |

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Effects and applications of *H. pylori* and its factors on GC immunotherapy

The 5-year survival rate of advanced GC patients is <30%. Although platinum-fluoropyrimidine combination chemotherapy is the standard first-line treatment for advanced GC, its low complete response rate and severe adverse reactions have limited its application (63, 166). Novel effective therapies are urgently required. For example, PD-1 inhibitor pembrolizumab received accelerated approval from the US Food and Drug Administration (FDA) in 2017 to treat recurrent advanced or metastatic gastric or gastroesophageal junction adenocarcinomas expressing PD-L1 (63, 167–169).

*Helicobacter pylori* is a class I carcinogen associated with GC (170–172). The overall survival of GC diagnosis is reported to be higher for patients with *H. pylori* infection (17). *Helicobacter pylori* infection induces PD-L1 expression and MDSC infiltration that mediate immune escape. HH signaling activated by *H. pylori* infection induces PD-L1 expression and tumor cell proliferation in GC, resulting in cancer cell resistance to immunotherapy (150). In addition, *Helicobacter pylori* and its virulence factors can act as antigens or adjuvants to enhance tumor immunity.

*Helicobacter pylori* virulence factors, such as CagA, VacA, blood-group antigen-binding adhesin gene (BabA), and *H. pylori* neutrophil-activating protein (HP-NAP), can act as antigens or adjuvants to enhance tumor immunity. The stimulation of autoantibodies during antigen processing and presentation and subsequent T-cell activation and proliferation improves the host immune status, which can kill cancer cells and even suppress metastasis (151). Moreover, *H. pylori* DNA vaccines encoding fragments of CagA, VacA, and BabA can induce Th1 shift to Th2 response in immunized BALB/c mice, which mimics the immune status of GC patients with chronic *H. pylori* infection. Stimulated CD3+ T cells inhibit the proliferation of human GC cells in vitro, and the adoptive infusion of CD3+ T cells inhibits the growth of GC xenografts in vivo (152).

HP-NAP is a major virulence factor in *H. pylori* infection and colony formation, and it can also act as a protective factor (173, 174). As a Toll-like receptor-2 (TLR2) agonist, HP-NAP can bind to TLR2 of neutrophils (161, 175). Furthermore, HP-NAP promotes the maturation of DCs with Th1 polarization and improves migration of mature DCs. Stimulating neutrophils and monocytes by HP-NAP induces IL-12 and IL-23 expression, thus shifting antigen-specific T cell responses from the Th2 to the Th1 phenotype which characterized by abundant IFN-γ and TNF-α expression (153). Vaccination with HP-NAP A subunit (NapA) promotes Th17 and Th1 polarization. Such vaccines have potential effects as an anti-*H. pylori* oral vaccine candidate and a mucosal immunomodulatory agent, which could be used in antitumor strategies (154).
### Effects and applications of *H. pylori* and its factors in other tumor immunotherapies

In addition to GC, the influence of *H. pylori* on other tumor immunotherapies is also paid much attention recently. *Helicobacter pylori* infection might disrupt the immune system and exert detrimental effects on the outcomes of cancer immunotherapies (19).

*Helicobacter pylori* seropositivity could reduce anti-PD-1 immunotherapy effect in non-small cell lung cancer (NSCLC) patients. *Helicobacter pylori* infection partially blocks the activities of ICIs and vaccine-based cancer immunotherapies. *Helicobacter pylori* suppresses the innate and adaptive immune responses of infected hosts and inhibits antitumor CD8+ T cell responses by altering the cross-presentation activity of DCs (19).

In contrast, a significantly high proportion of tumor-infiltrating T lymphocytes in *H. pylori*-positive de novo diffuse large B-cell lymphoma (DLBCL) patients preliminarily indicates a benign TME. Inflammation induced by *H. pylori* confers persistent activation of autoimmune Th cells, which would explain the benign TME (155). More researches are necessary to elucidate how *H. pylori* infection status influences the effects of tumor immunotherapies.

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**TABLE 3 Effects of *H. pylori* on tumor immunotherapy responses.**

| Cancer targeted by immunotherapy affected by *H. pylori* | Roles of *H. pylori* | Effects and applications |
|----------------------------------------------------------|----------------------|--------------------------|
| Gastric cancer                                           | Induces PD-L1 expression and MDSC infiltration (62–64, 150) | Mediates immune escape by cancer cells, causing resistance to immunotherapy |
|                                                          | Enhances tumor immunity by virulence factors (CagA, VacA and BabA) | Increases levels of CagA, VacA, and BabA autoantibodies, enhances antigen processing and presentation and T-cell activation and proliferation, and improves host immune status (151) |
|                                                          | HP-NAP               | DNA vaccine from CagA, VacA and BabA induces a shift from Th1 to Th2 response and activates CD8+ T cells to inhibit GC xenograft growth in vivo (152) |
|                                                          |                      | HP-NAP promotes maturation of DCs and stimulates neutrophils and monocytes to enhance antigen-specific T cell responses (153) |
|                                                          |                      | Oral NapA vaccination promotes Th17 and Th1 polarization, exerts anti-*H. pylori* and antitumor effects, enhances immune responses (154) |
| Non-small cell lung carcinoma                            | Decreases immune responses, inhibits antitumoral CD8+ T cell responses (19) | Partially blocks the activity of ICIs and vaccine-based cancer immunotherapy |
| DLBCL                                                    | Causes increased numbers of tumor-infiltrating T lymphocytes and persistent activation of autoimmune Th cells (155) | Results in a benign tumor immune microenvironment |
| Mouse subcutaneous hepatoma and sarcoma                 | rMBP-NAP promotes Th1 differentiation and increases the number of CD4+ IFN-γ-secreting cells (156) | rMBP-NAP has antitumor potential |
| Lung cancer                                              | rMBP-NAP increases the number of IFN–γ-secreting cells and CTL activity of PMBCs (157) | |
| Mouse metastatic lung cancer                            | rMBP-NAP restricts tumor progression by triggering antitumor immunity (158) | |
| Mouse breast and bladder cancers                        | HP-NAP enhances immune response and inhibits tumor growth (137, 159) | HP-NAP has antitumor potential |
| Melanoma                                                 | rHP-NAP promotes the maturation of dendritic cells in dendritic cell-based vaccines (160) | rHP-NAP has potential as an adjuvant |
| Mouse neuroendocrine tumor                              | HP-NAP improves median survival (161) | HP-NAP is a powerful source of immune-stimulatory agonists that can boost OV immunogenicity and enhance ICI effects (162, 163) |
| Mouse subcutaneous neuroblastoma                        | HP-NAP enhances antitumor efficacy of oncolytic vaccinia virus (164, 165) | |
| Glioblastoma                                             | MVs-NAP-uPAR improves tumor immunotherapy efficacy (163) | |
The immunomodulatory activity and potential applications of NAP in tumor immunotherapy have been investigated. Recombinant HP-NAP with the maltose-binding protein of *Escherichia coli* (rMBP-NAP) can mediate T helper lymphocytes differentiation into the Th1 phenotype and significantly increase the number of CD4+ IFN-γ-secreting T cells. This induces antitumor effects through a TLR-2-dependent mechanism in subcutaneous hepatoma and sarcoma mice model (156). rMBP-NAP can significantly increase peripheral blood mononuclear cells (PBMCs) that secrete IFN-γ, and prominently increases the cytotoxic activity of PBMCs derived from lung cancer patients (157). Treatment with rMBP-NAP restricts the progression of metastatic lung cancer in mice model by triggering antitumor immunity (158). A therapeutic nanocomplex of HP-NAP altered the production rate of cytokines and increase tumoricidal activities of the immune system, leading to decreased breast tumor growth in mice (137). Local administration of HP-NAP inhibits tumor growth by triggering tumor cell necrosis in bladder cancer mice model (159). Recombinant HP-NAP has potential effects as an adjuvant in DC-based vaccines for treating melanoma (160).

Because of its ideal immunogenicity, NAP has recently been applied as an immune adjuvant to enhance the antitumor immune response. When combined with oncolytic viruses (OVs), HP-NAP can activate the immune response. The intratumoral administration of adenovirus armed with secretory HP-NAP can improve the median survival rate of nude mice xenografted with neuroendocrine tumors (161). A recombinant vaccinia virus (VV) neuroblastoma-associated antigen disialoganglioside mimotope (GD2m)-NAP significantly improved therapeutic efficacy. *Helicobacter pylori*-NAP might help to overcome virus-mediated suppressive immune responses, resulting in improved anti-GD2 antibody production and a better therapeutic outcome (164, 165). Moreover, recombinant measles virus (MV)-NAP-urokinase-type plasminogen activator receptor (uPAR) can improve immunotherapeutic effects on glioblastoma with a better tumor prognosis and increased susceptibility to CD8+ T cell-mediated lysis. Overall, HP-NAP represents a potential immunostimulatory agonists which can boost the immunogenicity of OVs and enhance ICIs effects (162, 163).

In conclusion, *H. pylori* and its virulence factors could be closely related with personalized treatment strategies during tumor immunotherapies. The mechanisms of *H. pylori* infection in tumor immunotherapies requires further elucidation, and the translation of research findings to clinical applications should be accelerated.

**Summary**

This review summarized current knowledge of the effects of *H. pylori* on the immune microenvironment of GC and tumor immunotherapy responses. *Helicobacter pylori* elicits powerful immune responses during surviving and colonizing gastric mucosa. *Helicobacter pylori* has also developed several strategies to evade recognition and disrupt immune function. The constituents and functions of stroma are regulated by *H. pylori* and its virulence factors to facilitate its survival and colony. Persistent *H. pylori* infection can induce immune evasion and tumorigenesis.

The stroma provides TME for tumor initiation and development after *H. pylori* persistent infection. Immunotherapy targeting tumor-associated immune cells is more mature and improved, particularly immunotherapy targeting T cells, such as ICIs. PD-1 inhibitor pembrolizumab has received approval from the US FDA in 2017 to treat recurrent advanced or metastatic gastric or gastroesophageal junction adenocarcinomas (167). While some clinical trials targeting non-immune cells in TME such as CAFs, MSCs, have failed to show promising efficacy in cancer patients (176–178). The main reason might be a lack of deep understanding of the fundamental mechanisms of stromal cells and elements as well as a lack of reliable biomarkers to guide stroma-targeted therapies (176). Of course, because of the important roles of regulating the immune response in TME, targeting TAMs is getting more and more attraction. For example, targeting colony-stimulating factor 1 receptor (CSF1R) signaling and the CCL2-CCR2 axis are developing drugs (179, 180). And there are some developing drugs to reprogram TAMs from a pro-tumor phenotype to an anti-tumor phenotype and interrupt the bad cycle between TAMs and tumor cells (176, 177), such as agonistic anti-CD40 antibodies (181), PI3K inhibitors (182). These ongoing researches show good prospects in immunotherapy. Based on these, it seems that immunotherapy intervening tumor-associated immune cells may be more appropriate currently. However, we should also pay attention to the study of non-immune cells in TME. Further research on these cells may provide clues for developing new therapies in the future.

*H. pylori* infection might affect the tumor immunotherapy. Although *H. pylori* infection has been reported as a protective factor in GC immunotherapy while in NSCLC as a negative factor, the mechanisms and effect of *H. pylori* on GC immunotherapy still remains unclear (19, 183). *Helicobacter pylori* virulence factors can act as immunogens or adjuvants to elicit or enhance immune responses. Some *H. pylori* virulence factors such as HP-NAP, have been applied as adjuvants or combined with drugs in pan-tumor treatment to improve immunotherapeutic efficiency. The effects of *H. pylori* in TME should be further explored, and clinical applications should be performed to select the proper features of population for better immunotherapy benefits.

**Author contributions**

RD and HZ searched the literature and wrote the manuscript. HC and ML re-checked the literature. YS and SD.
designed this study and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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