The role of non-coding RNA in the diagnosis and treatment of *Helicobacter pylori*-related gastric cancer, with a focus on inflammation and immune response

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Helicobacter pylori (*H. pylori*) is one of the globally recognized causative factors of gastric cancer (GC). Currently, no definite therapy and drugs for *H. pylori*-related GC have been widely acknowledged although *H. pylori* infection could be eradicated in early stage. Inflammation and immune response are spontaneous essential stages during *H. pylori* infection. *H pylori* may mediate immune escape by affecting inflammation and immune response, leading to gastric carcinogenesis. As an important component of transcriptome, non-coding RNAs (ncRNAs) have been proven to play crucial roles in the genesis and development of *H. pylori*-induced GC. This review briefly described the effects of ncRNAs on *H. pylori*-related GC from the perspective of inflammation and immune response, as well as their association with inflammatory reaction and immune microenvironment. We aim to explore the potential of ncRNAs as markers for the early diagnosis, prognosis, and treatment of *H. pylori*-related GC. The ncRNAs involved in *H. pylori*-related GC may all hold promise as novel therapeutic targets for immunotherapy.

KEYWORDS

Helicobacter pylori, non-coding RNA, *H. pylori*-related GC, inflammation, immune response, microRNA

Introduction

Gastric cancer (GC) is one of the leading malignancies in terms of morbidity and mortality worldwide, which has attracted extensive attention among global health problems (1). Its high incidence and mortality are mainly attributed to some unclear pathogenesis. The chronic infection of *Helicobacter pylori* (*H. pylori*) has been well-accepted as one of the multiple pathogenic factors of GC. It has been listed as a primary carcinogen by the International Agency for Cancer (2, 3). Chronic *H. pylori* infection can result in diseases such as gastritis, gastric ulcer and GC over time, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma may also develop in some patients (4–7). However, the specific mechanism of *H. pylori* infection on gastric carcinogenesis remains unidentified in spite of the known causality between them. Exploration for the mechanism would be conducive to GC prevention and treatment.

As a key element of pathogenic factors for *H. pylori*-related GC, the virulence factors of *H. pylori* associated with immune response mainly consist of cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), and *H. pylori* neutrophil-activating protein (HP-NAP), etc. (8). Among them, CagA was reported to exist in more than 60% of *H. pylori* strains considered to be a strong activator of NF-κB and a major mediator of carcinogenesis (9). CagA can not only bind to NF-κB *via* beta-catenin but also independently affect NF-κB and produce inflammatory factors such as IL-8 to mediate immune response (9, 10). VacA inhibits capital histocompatibility complex class II (MHC II)-dependent pathways and releases pro-inflammatory factors including IL-1β, IL-6, IL-10, and tumor necrosis factor-alpha (TNFα) by forming vacuoles within macrophages, thus inducing immune escape and protecting *H. pylori* (11). Unlike VacA, HP-NAP up-regulates MHC II, promotes Th1 immune response, induces the expression of IL-12 and IL-23 in neutrophils and monocytes, and triggers ROS release to destroy epithelial cells (12, 13). The recognition of lipopolysaccharide (LPS) from *H. pylori* by toll-like receptors (TLRs, mainly TLR4 and TLR2) in human body could activate the NF-κB pathway and promote the chemotaxis of immune cells such as neutrophils and dendritic cells to release large amounts of inflammatory factors attempting to phagocytose *H. pylori*. However, the specific virulence factors of *H. pylori* could protect themselves from phagocytosis initiated by innate immune response. Consequently, the large quantity of inflammatory factors have to accumulate at *H. pylori* colonization sites and cause a long-term inflammation in epithelium, leading to chronic gastritis and even GC (14).

The unique virulence factors enable *H. pylori* to escape from the eradication by immune system and colonize in gastric mucosa making carcinogenic effects. After *H. pylori* infection, innate immunity is first activated to release pro-inflammatory factors and immune cells intending to phagocytose and eliminate *H. pylori*, then local immune microenvironment is altered. Once the changes fail to resist the pathogenic effects of virulence factors, *H. pylori* could colonize in gastric mucosa, break through the barrier and survive in the deep site of stomach chronically, resulting in gastritis, gastric ulcer and even GC over time. Therefore, inflammation and immune response are essential parts during the initiation of *H. pylori*-related GC.

Mounting studies about *H. pylori*-related GC have focused on non-coding RNAs (ncRNAs). NcRNAs consist of microRNAs (miRNAs), long ncRNAs (lncRNAs), circular RNAs (circRNAs), small nucleolar RNAs (snoRNAs), and piRNAs (15). In the early stage after discovery, ncRNAs were regarded as useless "garbage" in body due to the lack of capability to encode proteins. With the depth of research, however, the important regulatory function of ncRNAs in many basic cellular processes has been gradually revealed including development, differentiation, proliferation, transcription, post-transcriptional modification, immune regulation, cell apoptosis, and metabolism (16). Despite the inability of ncRNAs to directly encode proteins, more than 60% of their downstream target genes have the competence (17). It has been suggested that rare ncRNAs can independently function in diseases. They usually interact with each other to construct powerful networks and affect many proteins determining cell fates as well as specific cellular biological process by regulating functional stability. The complex interactions make the dysregulation of ncRNAs quite common in cancer (18–20). The immune inflammatory response occurring in *H. pylori*-related GC can alter the expression patterns of ncRNAs, thereby affecting the expression of downstream proteins or target genes and GC biological behaviors.

In the present review, we integrated the articles studying ncRNAs with immune inflammation in *H. pylori*-related GC, summarize the research frontiers of ncRNAs in this field and explore the potential of ncRNAs as diagnostic and prognostic markers for *H. pylori*-related GC, aiming to provide theoretical basis for further investigation of ncRNAs on the immune direction in *H. pylori*-related GC. The immunization of ncRNAs in *H. pylori*-related GC might give a new sight for GC diagnosis and treatment.

MiRNAs and *Helicobacter pylori*-related gastric cancer

MiRNAs are short ncRNAs with approximately 22 nucleotides in length. They can inhibit the expression or function of downstream target genes by inducing degradation or translational inhibition through binding to the 3′ untranslated region (3′-UTR) of target genes (especially mRNAs) with their 5′ ends (21). MiRNAs are the most extensively studied ncRNAs so far. The association of miRNAs with *H. pylori*-related GC has been gradually emphasized on immune inflammation. TLRs

could be activated by LPS from *H. pylori*, and aberrant TLRs may promote the expression of some miRNAs. MiRNAs can also affect the NF-κB pathway by regulating TLRs expression and the TLR signaling pathway in turn, inducing the release of pro-inflammatory factors, transcription factors and cascades (22, 23). The structure of LPS could also be modulated by small RNAs to influence the immune recognition in host thereby enhancing *H. pylori* resistance (24). Therefore, miRNAs are shown to have the potential to serve as detective markers for early diseases (25–28).

MiR-155

MiR-155 has emerged as a key factor in innate immunity and inflammatory reaction. *H. pylori* could induce miR-155 in gastric epithelial cells and gastric mucosa, which has been widely reported to damage *H. pylori* by triggering immune response (23, 29–33). The induction of miR-155 in T cells mediated by *H. pylori* might be based on a cAMP-Foxp3-dependent manner (34). MiR-155 promotes the release of inflammatory factors including TNF-α, IL-6, and IL-23 in exosomes from macrophages infected with *H. pylori* and simultaneously increases the expression of CD40, CD63, CD81, and MCH-I, suggesting that miR-155 may regulate *H. pylori*-induced inflammation in host cells *via* exosomes (35). MiR-155 can also promote *H. pylori* elimination by inducing autophagy to enhance the sterilization ability of host to intracellular *H. pylori* (36). The association of miR-155 with immunity in *H. pylori* infection appears to be proved in mice. The generation of miR-$155^{-/-}$ mice might be owing to an inherent defect in T cells that impairs specific Th1 and Th17 cells making them disabled to proliferate, produce IFN-γ and IL-17, thus control *H. pylori* infection effectively (37). In addition, miR-155 is up-regulated in macrophages during *H. pylori* infection dependent on TLR and type IV secretion system (T4SS), inhibiting cell apoptosis caused by DNA damage (38).

However, some researchers believed that miR-155 negatively regulated inflammatory reaction and reduced immune response of body to protect *H. pylori*. Xiao et al. (39) found that the induction of miR-155 by *H. pylori* was dependent on the activation of NF-κB and AP-1 pathways. After miR-155 overexpression, a down-regulation was demonstrated in IkappaB kinase epsilon (IKK-ε), Fas-associated death domain (FADD) as well as Sma- and Mad-related protein 2 (SMAD2), which negatively regulated the release of IL-8 and growth-related oncogene-α (GRO-α). Except for miR-155, myeloid differentiation protein 88 (MyD88) was also observed to be involved in the negative regulation of *H. pylori*-induced inflammatory reaction as a target gene of miR-155 (40).

The diverse roles of miR-155 in *H. pylori*-induced immune inflammatory response mentioned above indicated it as a potential marker for *H. pylori*-related GC.

MiR-223

MiR-223 was also suggested to be involved in pathways associated with innate immunity and inflammatory reaction in patients with *H. pylori* infection (41–43). CagA of *H. pylori* may induce miR-223-3P expression through the NF-κB pathway. And miR-223-3p can directly target AT-rich interactive-domain 1A (ARID1A), a tumor suppressor protein with ATP enzymatic activity, to promote GC proliferation and migration. Therefore, *H. pylori* might participate in CagA-mediated biological effects in GC cells *via* the NF-κB/miR-223-3p/ARID1A axis (44). MiR-223-3p and IL-10 secreted by macrophages exert inhibitory effects on pro-IL-1β and inflammasome NLRP3 both secreted by monocytes during *H. pylori* infection (32, 45). Furthermore, the mucosal expression level of miR-223 was significantly decreased following with the disappearance of neutrophils from gastric mucosa in patients after *H. pylori* eradication (46). A recent study, however, showed that miR-233 expression decreased in *H. pylori*-associated autoimmune atrophic gastritis and multifocal atrophic gastritis. Hence, the anti-inflammatory function of miR-233 might vary with different microenvironments (47). These findings made miR-223 also a potential marker for the diagnosis or treatment of *H. pylori*-related GC.

MiR-375

MiR-375 appears to be closely associated with immune inflammatory response in *H. pylori*-related GC. It was shown to be down-regulated after *H. pylori* infection accompanied by the activation of JAK2-STAT3 (48–51). Janus kinase 2 (JAK2) was identified as a target gene of miR-375, and miR-375 could negatively regulate the expression of programmed cell death-ligand 1 (PD-L1) in GC through the JAK2/STAT3 signaling pathway (50). *H. pylori* may affect the JAK2-STAT3 pathway releasing cytokines including IL-6, IL-10, and VEGF by down-regulating miR-375, inhibit the maturity of dendritic cells, reduce $CD4^+$ and $CD8^+$ T cells, then inhibit immune response mediating the immune escape of *H. pylori* to promote gastric carcinogenesis (52). Moreover, the regulation of JAK2-STAT3 signaling by miR-375 could release IL-1β, IL-6, IL-8, and TNF-α by activating downstream target genes BCL-2 and TWIST1, which promotes tumor transformation and gets involved in *H. pylori*-induced cell proliferation and migration (53). Rossi et al. found that the levels of IL-6, IL-12A, and IL-2 were significantly elevated in *H. pylori*-positive patients followed by the down-regulation of miR-103, miR-181c, miR-370, and miR-375 (54). All above-mentioned results suggested that miR-375 participated in *H. pylori*-related GC by regulating immune response.

MiR-146

MiR-146 might be involved in the development of *H. pylori*-related gastric diseases *via* the NF-KB pathway. *H. pylori* infection could trigger inflammatory reaction of body and induce the production of IL-17A, GRO-α, IL-8, and miR-146α in GC cells successively. For its mechanism, IL-17A might mediate miR-146α to regulate inflammatory reaction in an NF-κB-dependent manner during *H. pylori* infection (55). Other than *H. pylori*-related GC, miRNAs especially miR-146a and miR155 also received much attention in *H. pylori*-related pediatric gastritis, which were likely to be associated with its prognosis (56, 57).

Other miRNAs

Most miRNAs involved in the regulation of *H. pylori*-related GC had association with the NF-κB pathway. The decrease of miR-204 level induced by *H. pylori* infection could up-regulate the downstream target gene BIRC2, enhance the activity of BIRC2/TNF-α/NF-κB signaling pathway, thus promote angiogenesis and metastasis of GC cells, leading to poor prognosis of *H. pylori*-related GC patients (58). *H. pylori* infection was reported to induce miR-18a-3P and miR-4286 expression in GC through TLR4/NF-κB molecules related to immune recognition, inhibit the expression of downstream target gene BARAP1, thereby participate in innate immune response of body and inflammatory pathways associated with NF-κB (59). *H. pylori* activates NF-κB and reduces miR-218 expression to increase the level of downstream target gene called epidermal growth factor receptor-amplified and overexpressed protein (ECOP) promoting cell proliferation. Accordingly, Gao et al. believed that miR-218 could be considered as a therapeutic target for *H. pylori*-related GC. The inhibition of NF-κB by increasing miR-218 expression level artificially might become a kind of therapy to prevent the progression from precancerous lesion to cancer (60). In gastric epithelial cells infected with *H. pylori*, Tip-α inhibits miR-3178 targeting TRAF3 to increase TNF-α and IL-6 activating NF-κB to promote GC cell proliferation (61). Let-7b targeting TLR4 was shown to decrease in gastric epithelial cells infected with *H. pylori*. The knockdown of TLR4 concurrent with let-7b overexpression could reduce the expression of downstream genes associated with immune inflammatory response including NF-κB, MyD88, NF-κB1/p50, and RelA/p65 (62). Lin et al. found that serum miR-130b level was elevated in human and mice after *H. pylori* infection activating the NF-κB pathway positively correlated with myeloid-suppressor Schlafen4 (Slfn4). Further research revealed that gastric SLFN4⁺ cells infected with *H. pylori* might induce miR-130b and exhibit a T cell suppressive phenotype resulting in *H. pylori*-induced gastric metaplasia, tumor formation and growth (63). Based on these findings, *H. pylori* infection may activate the NF-κB pathway by regulating miRNAs to affect biological function facilitating the development of inflammation and cancer.

Additionally, miRNAs may also influence *H. pylori*-related GC by regulating PD-1/PD-L1 involved in immune response. PD-L1 might be a downstream target of miR-140. MiR-140 could increase IFN-γ and TNF-α levels, inhibit the PD-L1 and mTOR signaling pathways, and raise CD8⁺ T cells, thus inhibiting the proliferation of *H. pylori*-positive GC to exert anti-cancer roles (64). Xie et al. (65) reported that *H. pylori* could regulate B7-H1 binding to PD-1 by inhibiting miR-152 and miR-200b in GC cells, thereby suppress T cell proliferation and immune response. *H. pylori* might also alter the levels of miR-326 and miR-663 in CD4⁺ T cells (66).

Methylation has been suggested to be another mechanism by which miRNAs affect *H. pylori* through immune inflammatory response. The extract of *Celastrus orbiculatus* (COE) regulates *H. pylori*-induced inflammatory response by inhibiting miR-21 expression and the methylation level of target gene programmed cell death 4 (PDCD4) (67). Furthermore, the tumor suppressor factor miR-124 silences spermine oxidase (SMOX) in *H. pylori*-related GC *via* DNA methylation (68). JARID1B is a histone demethylase and its up-regulation is associated with immune cell infiltration in *H. pylori*-related GC. Therefore, the miR-29c/JARID1B/cyclinD1 axis could be a novel therapeutic pathway for GC (69).

Some other miRNAs were also indicated to be associated with immunity or inflammation in *H. pylori*-related GC. *H. pylori* up-regulates the immune receptor CD300E by down-regulating miR-4270 to enhance the pro-inflammatory potential and impair the sterilization ability of macrophages (70). Chronic inflammation caused by *H. pylori* infection was shown to increase CD44V9 by down-regulating miR-328 in gastric mucosa (71). Except for miR-223-3p mentioned above, miR-22 can also directly target NLRP3, reduce inflammasomes levels and maintain the homeostasis of gastric microenvironment. *H. pylori* disrupts microenvironment homeostasis by inhibiting the regulation of miR-22 on downstream factor NLRP3 (72). In conclusion, miRNAs could regulate the expression of inflammatory factors and suppress immune response after *H. pylori* infection, contributing to the immune escape of *H. pylori* and ultimately GC (**Table 1** and **Figure 1**).

LncRNAs and *Helicobacter pylori*-related gastric cancer

LncRNAs are long ncRNAs with more than 200 nucleotides in length. They play vital roles in cellular process despite not encoding proteins (73, 74). LncRNAs have been widely proven to be associated with GC genesis and development by affecting biological function (75).
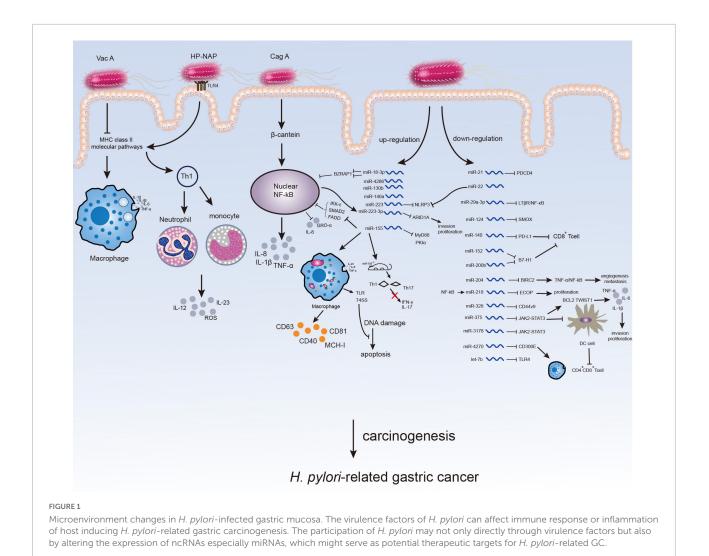
TABLE 1   The regulation of miRNAs on inflammation and immune response in *H. pylori*-related gastric cancer.

MicroRNA(s)	Expression	Patients	Cell line	Target	Mechanism of action	References
miR-155	Up		RAW264.7		Promoted the expression of TNF-a, IL-6, IL-23, CD40, CD63, CD81, MCH-I, MyD88, and NF-κB	(35)
miR-155	Up				miR-155 -/- mice produce fewer IFN-γ and IL-17 than wt-T cells and do not differentiate into Th1 or Th17 cells, and do not cause immunopathology.	(37)
miR-155	Up	22	GES-1, AGS, MKN45 (HEK) 293	IKK-ε, SMAD2, and FADD	Down-regulate NF-κB and AP-1 pathway to negatively regulated IL-8 and GRO-α.	(39)
miR-155	Up		MKN74, AGS	The protein kinase A inhibitor alpha (PKIalpha)	miR-155 -cAMP-Foxp3 axis in T cells	(34)
miR-155	Up		GES-1		Induce the autophagy to decrease the survival of intracellular *H. pylori*	(36)
miR-155	Up		AGS and (HEK) 293 cells	MyD88	Reduce IL-8 production induced by *H. pylori* infection.	(40)
miR-223	Up	22	AZ-521		Increase the neutrophil and/or mononuclear cell infiltration	(46)
miR-223-3p	Up	50	SNU, AGS, MGC-803, and MKN1	ARID1A	NF-κB/miR-223-3p/ARID1A axis is involved in CagA-induced cell proliferation and migration	(44)
miR-223	Up		THP-1, AGS	NLRP3	Increase the copious amount of IL-10, IL-1β	(45)
miR-22	Down			NLRP3	Riggers' uncontrolled proliferation of epithelial cells and the emergence of GC	(72)
mir-375	Down		BGC823, GES-1, and MFC	JAK2-STAT3	Promote the secretion of IL-6, IL-10, and VEGF, leading to immature differentiation of DCs and induction of gastric cancer.	(52)
miR-375	Down		BGC-823, AGS, SGC-7901, and MKN-45	JAK2	miR-375/JAK2-STST3 is involved in *H. pylori*-induced inflammation to induce IL-8 and TNF-α and promotes neoplastic transformation by affecting the expression of BCL-2 and TWIST1	(53)
miR-375	Down	31			Up-regulation of TNFA, IL6, IL12A, IL2, and TGF-β-RII.	(54)
miR140	Down	15	AGS, MGC803 SGC7901, BGC823, MKN45	PD-L1	Suppress GC by targeting immune checkpoint molecule PD-L1.	(64)
miR-200b	Down	76	AGS	B7-H1	*H. pylori* promoted B7-H1 expression which binds to PD-1 and inhibited miR-152 and miR-200b expression to promote gastric cancer	(65)
miR-152						
miR-204	Down	26	AGS, BGC-823, SGC-7901, and MGC-803	BIRC2	miRNA-204 leads to enhanced BIRC2 expression level and BIRC2/TNF-a/NF-kB signaling pathway activities, which promoted angiogenesis and metastasis of gastric cancer cells.	(58)
miR-18a-3p	Up		AGS, N87, and MKN45	BZRAP1	miR-18a-3p and miR-4286 activated the NF-κB transcription factor to increase cancer cell proliferation and motility and both inhibited expression of BZRAP1, but TAK-242 (TLR4 inhibitor) blocked this effect.	(59)

(Continued)

TABLE 1 (Continued)

MicroRNA(s)	Expression	Patients	Cell line	Target	Mechanism of action	References
miR-4286						
miR-218	Down		AGS and MKN45	ECOP	miRNA-218 inhibits NF-κB activation by decreasing ECOP expression, increasing cell proliferation, and inhibiting cell apoptosis.	(60)
miR-146a	Up		SGC-7901		miR-146a inhibits the inflammatory responses induced by IL-17A during the infection of Hp	(55)
miR-3178	down		GES-1, SGC7901, and MGC803	TRAF3	Tip-α might activate NF-κB to promote inflammation such as TNF-α and IL-6, and carcinogenesis by inhibiting miR-3178 expression, which directly targets TRAF3	(61)
miR130b	Up	21–63			MiR130b induce T-cell suppressor phenotype and promoted Helicobacter-induced metaplasia	(43)
miR-21	Down			PDCD4	COE could inhibit microRNA-21 (miR-21) expression and target PDCD4 and induce inflammatory factors such as IL-6, IL-8, and TNF-α.	(67)
miR-124	Down		AGS	SMOX	miR-124 through the inhibition of SMOX-mediated DNA damage in the etiology of H. pylori-associated gastric cancer.	(68)
miR-4270	Down	10		CD300E	HP modulating the expression of the immune receptor CD300E through miR-4270	(70)
miR-328	Down	54	AGS.AGS cells were treated with TNF-α, interleukin-1b (IL-1b), or H2O2	CD44v9	High CD44v9 expression is significantly associated with low miR-328 expression can avoid cell death caused by various stress inducers and inhibit gastric cancer development.	(71)
miR-29a-3p	Down	82	GES-1, MGC-803, AGS, MKN-45, SGC-7901 and HGC-27	LTβR/NF-κB	HOXA-AS3/miR-29a-3p/LTβR/NF-κB regulatory axis contributes to the progression of GC	(83)
let-7	Down			TLR4	let-7b downregulate TLR4 and attenuated NF-κB, MyD88, NF-κB1/p50, RelA/p65, IL-8, COX-2, and CyclinD1	(62)

It has been preliminarily explored for the regulatory relationship with mechanisms of lncRNAs in *H. pylori*-related GC. However, few studies have focused on immunity and inflammation, which is ought to be future research direction in this field. LncRNAs were demonstrated to be implicated in viral infection recently (76). In *H. pylori*-infected GC, a decreased expression of TNF-α, IL-1β, and IL-8 was detected after knockdown of plasmacytoma variant translocation 1 (lncPVT1) and the migration of GC cells was inhibited, suggesting that lncPVT1 might activate immune function to affect GC caused by *H. pylori* (77). Similar to this result, another study reported that the overexpression of lncRNA H19 induced inflammatory reaction *via* the NF-κB pathway, released pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, and IL-8, then promoted GC cell proliferation, migration and invasion infected with *H. pylori* (78). Besides, circulating lncRNA H19 expression was significantly increased in *H. pylori*-positive peptic ulcer patients and further increased in GC patients statistically positively correlated with the levels of TNF-α, IFN-γ, and gastrin. Hence, lncRNA H19 could be applied to distinguishing GC from peptic ulcer with positive *H. pylori* (79). LncRNA SGK1 was found to be elevated in T cells of *H. pylori*-related GC, induce Th2 and Th17 cells, reduce Th1 cell differentiation through the SGK1/JunB signaling pathway and be associated with poor prognosis of *H. pylori*-infected GC (80). LncRNAs may also affect the progression of *H. pylori*-related MALT. It was shown that lncRNA GHRLOS exhibited significant change in gastric MALT patients, which had differential expression both in *H. pylori*-positive gastritis and GC tissue (81). That might be a sound evidence for lncRNAs as important factors in the development of gastric malignancies. The above findings indicated that lncRNAs might participate in

FIGURE 1

Microenvironment changes in *H. pylori*-infected gastric mucosa. The virulence factors of *H. pylori* can affect immune response or inflammation of host inducing *H. pylori*-related gastric carcinogenesis. The participation of *H. pylori* may not only directly through virulence factors but also by altering the expression of ncRNAs especially miRNAs, which might serve as potential therapeutic targets for *H. pylori*-related GC.

gastric malignant tumors induced by *H. pylori* with the potential to be predictive biomarkers.
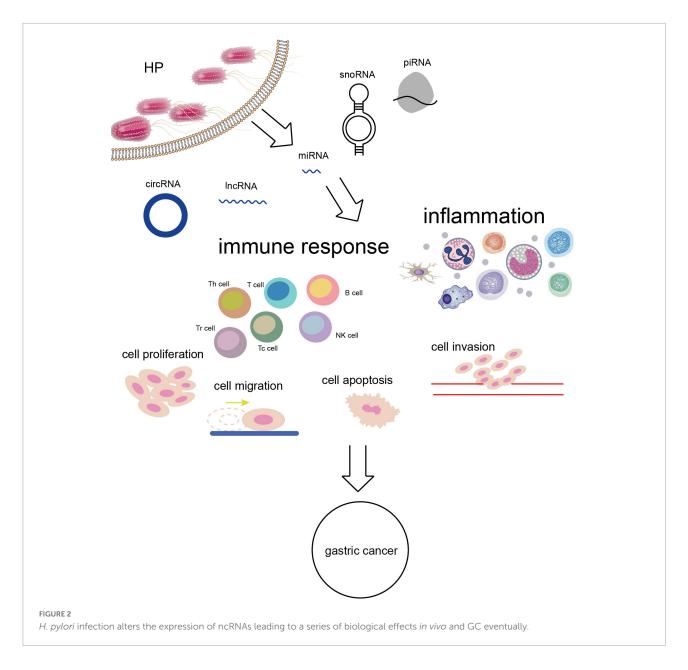
Other than independent effects, lncRNAs can also interact with miRNAs forming ceRNA networks to jointly regulate *H. pylori*. MiR-375 has been identified as an inhibitor of *H. pylori*-related GC, and the expression of lncRNA SOX2OT was down-regulated after miR-375 overexpression, suggesting the relationship of co-regulation between lncRNAs and miRNAs on *H. pylori*-related GC (82). LncRNA HOXA-AS3 is elevated in GC relevant with *H. pylori* infection. It negatively regulates miR-29a-3p and inhibits the downstream target gene LTβR regulating the NF-κB pathway to affect GC cell migration, proliferation, metastasis and invasion (83). CDK2, a negative regulator of T cells, was determined to form a cross-network with lncRNAs and miRNAs integrating lncRNA-TF-mRNA and ceRNA networks related to *H. pylori*, regulating immune microenvironment with pathogenic roles of *H. pylori* (84). A ceRNA network constituted by the lncRNA-RP11-1094M14.8/miR-1269a/CXCL9 axis was revealed to be linked

to a variety of immune cells *via* CXCL9, making it a potential target for GC with different degrees of immune cell infiltration (85).

LncRNAs can not only influence immune function directly by themselves but also affect the carcinogenesis of *H. pylori* by forming ceRNA networks with miRNAs to jointly regulate *H. pylori*-related tumor microenvironment.

CircRNAs and *Helicobacter pylori*-related gastric cancer

CircRNAs are recognized to form a covalently closed loop structure by unique reverse splicing with the lack of terminal 5′ cap and 3′ polyadenylated tail (86). Due to their structural property, circRNAs have a high level of stability and tissue-specificity in physiological environment of eukaryotes. Most circRNAs are aberrantly expressed in pathological conditions

FIGURE 2
H. pylori infection alters the expression of ncRNAs leading to a series of biological effects *in vivo* and GC eventually.

such as cancer (87), which are also potential markers for disease progression.

The regulatory relationship of circRNAs with GC has been extensively studied. In recent years, circRNAs have shown promise as biomarkers for cancer diagnosis and prognosis especially for early cancer detection (88, 89). CircSOBP is closely associated with GC metastasis and poor survival of 5-year follow-up (90). CircARID1A regulates GC proliferation by forming an RNA-protein ternary complex with IGF2BP3 and SLC7A5, thus the circARID1A-IGF2BP3-SLC7A5 axis could be a novel therapeutic target for GC (91). The circ0008287/miR-548c-3p/CLIC1 axis promotes cell apoptosis and immune escape by impairing the function of CD8 + T cells in GC (92). CircEIF4G3 can inhibit GC cell proliferation and metastasis by

regulating the miR-4449/SIK1 axis (93). Moreover, circ0002360 up-regulates PDLIM4 expression by sponging miR-629-3p (94). All these reports suggested the great potential of circRNAs to be prognostic biomarkers and therapeutic targets for GC.

However, the association of circRNAs with *H. pylori* and *H. pylori*-related GC remains rarely explored. Only a few studies presented that circRNAs might regulate the biological function or prognosis of *H. pylori*-related GC independently or by networks with miRNAs (95). *H. pylori* infection was found to increase circFNDC3B expression. In early gastric cancer (EGC) patients treated with endoscopic submucosal dissection (ESD), the expression of miR-942 and miR-510 was suppressed while their target genes CD44 and CDH1 were increased in the group with high circFNDC3B expression when compared with the

low expression group, which contributed to a higher recurrence rate in EGC patients consequently (96). CD44 was considered as a stem cell-like cancer cell marker affecting EGC initiation with *H. pylori* infection (97). Earlier studies also confirmed that circFNDC3B could mediate GC cell migration and invasion by promoting epithelial-mesenchymal transition (EMT) (98). Additionally, *H. pylori* can upregulate circMAN1A2 expression in GC cells, and circMAN1A2 may promote proliferation, migration and invasion of *H. pylori*-induced GC by sponging miR-1236-3p to increase MTA2 expression (99).

In spite of the previous research on circRNAs associated with *H. pylori*-related GC, further investigations are needed to support circRNAs in serving as diagnostic biomarkers and therapeutic targets for *H. pylori*-related GC.

Other ncRNAs and *Helicobacter pylori*-related gastric cancer

Except for the highly studied miRNAs, lncRNAs, and circRNAs, ncRNAs also contain snoRNAs and piRNAs. The research on them could also be conducive to deeply understanding the association of ncRNAs with *H. pylori*-related GC although the known mechanisms are limited. *H. pylori* was suggested to be delivered into host cells by two snoRNAs enriched in outer membrane vesicles of bacteria including sR-2509025 and sR-989262, reduce LPS stimulation and inhibit IL-8 secretion, thereby mediating immune escape (100). The association of other ncRNAs with *H. pylori*-related GC worth further exploration (**Figure 2**).

Summary

NcRNAs play critical roles in transcriptome with regulatory function in all aspects of physiological process, pathological process and disease progression. As one of the important pathogenic factors of GC, the association of *H. pylori* with ncRNAs has been extensively studied. NcRNAs have been clarified as a key link from persistent infection of *H. pylori* to GC and to make profound impacts despite the specific mechanisms to be confirmed. The regulation of ncRNAs on the immune microenvironment of body after *H. pylori* infection could be a therapeutic target for *H. pylori* in the future. The present review elaborated the bridge role of ncRNAs between *H. pylori* and GC from the perspective of immune inflammatory response, indicating that ncRNAs held promise as biomarkers for the early diagnosis, prognosis, and treatment of *H. pylori*-related GC. However, relevant exact molecular mechanisms need to be verified and more clinical data should be involved as additional evidence to the prognosis study, aiming to improve the survival and life quality of *H. pylori*-related GC patients.

Author contributions

B-GW, Y-KL, and ZL conceived and designed this study and revised the manuscript. A-RL and L-YJ collected the data for the review. A-RL and Z-WY wrote the manuscript. All authors contributed to the article and approved the submitted version.

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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