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REVIEW

Helicobacter pylori and microRNAs: Relation with innate immunity and progression of preneoplastic conditions

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Abstract

The accepted paradigm for intestinal-type gastric cancer pathogenesis is a multistep progression from chronic gastritis induced by *Helicobacter pylori* (*H. pylori*) to gastric atrophy, intestinal metaplasia, dysplasia and ultimately gastric cancer. The genetic and molecular mechanisms underlying disease progression are still not completely understood as only a fraction of colonized individuals ever develop neoplasia suggesting that bacterial, host and environmental factors are involved. MicroRNAs are noncoding RNAs that may influence *H. pylori*-related pathology through the regulation of the transcription and expression of various genes, playing an important role in inflammation, cell proliferation, apoptosis and differentiation. Indeed, *H. pylori* have been shown to modify microRNA expression in the gastric mucosa and microRNAs are involved in the immune host response to the bacteria and in the regulation of the inflammatory response. MicroRNAs have a key role in the regulation of inflammatory pathways and *H. pylori* may influence inflammation-mediated gastric carcinogenesis possibly through DNA methylation and epigenetic silencing of tumor suppressor microRNAs. Furthermore, microRNAs influenced by *H. pylori* also have been found to be involved in cell cycle regulation, apoptosis and epithelial-mesenchymal transition. Altogether, microRNAs seem to have an important role in the progression from gastritis to preneoplastic conditions and neoplastic lesions and since each microRNA can control the expression of hundreds to thousands of genes, knowledge of microRNAs target genes and their functions are of paramount importance. In this article

we present a comprehensive review about the role of microRNAs in *H. pylori* gastric carcinogenesis, identifying the microRNAs downregulated and upregulated in the infection and clarifying their biological role in the link between immune host response, inflammation, DNA methylation and gastric carcinogenesis.

Key words: *Helicobacter pylori*; MicroRNA; Gastric cancer; Inflammation; DNA methylation; Preneoplastic conditions; Stomach neoplasms; Immune response

Core tip: *Helicobacter pylori* (*H. pylori*) are involved in the progression of gastric preneoplastic conditions and gastric carcinogenesis although the clear genetic and molecular mechanisms are not completely clear. MicroRNAs may have an important role in the development of *H. pylori* mediated pathology since they can alter the expression of hundreds to thousands of genes. In this article we present a comprehensive review about the microRNAs that are altered in *H. pylori* infection and the biological consequences of this alteration, linking the inflammatory and immune host response with the progression of preneoplastic conditions and gastric carcinogenesis.

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INTRODUCTION

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer-related death[1]. *Helicobacter pylori* (*H. pylori*), a microaerophilic gram-negative bacteria that colonizes the gastric epithelium of over 50% of the world's population, has been identified as a definite (type Ⅰ) carcinogen by the World Health Organization and is thought to contribute for approximately 75% of GCs[2].

The accepted paradigm for the pathogenesis of intestinal-type GC is a multistep progression from inflammation/chronic gastritis induced by *H. pylori* to gastric atrophy, intestinal metaplasia, dysplasia and ultimately adenocarcinoma, as first suggested by Correa[3]. *H. pylori* are responsible for the initial stages of gastritis and atrophy and contributes to the progression to preneoplastic conditions/lesions and ultimately GC, but the molecular mechanisms underlying disease progression are still not completely understood. Besides, only a fraction of colonized individuals ever develop neoplasia, suggesting that strain-specific bacterial virulence factors, host responses and environmental factors may influence cancer risk.

MicroRNAs (miRNAs) are noncoding RNAs with 18-24 nucleotides which can cause mRNA degradation or translational inhibition, influencing the transcription and expression of various genes and playing an important role in inflammation, cell proliferation, apoptosis and differentiation. The biogenesis of miRNAs is initiated in the nucleus by the RNase Ⅲ enzyme Drosha[4]. Drosha and its cofactor Pasha (DGCR8) cleave primary miRNA transcripts generating precursor miRNAs of about 60 nucleotides (pre-miRNA) which are subsequently transported out of the nucleus to the cytoplasm for further processing into mature miRNA by Dicer, a cytoplasmic RNase Ⅲ[5,6]. Mature miRNAs are single-stranded RNA, 18-24 nucleotides long, which down-regulate specific gene products by translational repression of their target mRNAs *via* direct binding to 3' untranslated regions (3'-UTR) or by directing mRNA degradation *via* binding to perfectly complementary sequences[7].

Over one thousand microRNAs have been identified and each miRNA may regulate the expression of hundreds to thousands of target genes and it is estimated that 30%-92% of human genes are regulated by miRNA[8]. Identification of these target genes is critical to understand the biological role of each miRNA since miRNAs can influence the expression of tumor suppressor genes and oncogenes and thus are involved in proliferation and apoptosis, possibly contributing to initiation and progression of malignancy. In gastrointestinal cancers some miRNAs are downregulated suggesting that these downregulated miRNAs act as tumor suppressors (*e.g.,* mir-15b and mir-16, which target anti-apoptotic Bcl-2, are downregulated in GC)[9]. On the other hand, some miRNA are overexpressed in gastrointestinal cancers, suggesting their role as oncogenes (*e.g.,* miR-155, which represses expression of pro-apoptotic TP53INP1, is overexpressed in mucosa-associated lymphoid tissue lymphoma)[10].

H. pylori can affect the expression of various miRNAs which may induce epigenetic deregulation of oncogenes and tumor suppressor genes and may represent the bridge between *H. pylori*-gastritis and GC[11,12]. *H. pylori* possess a set of virulence factors necessary to successfully colonize the gastric mucosa and establish chronic infection. The vacuolating cytotoxin (VacA) exhibits vacuolating activity and is coded by the gene *vacA*, which is present in all *H. pylori* strains. VacA can induce apoptosis of host cells and suppress proliferation of T and B-lymphocytes, contributing to the ability of *H. pylori* to establish chronic infection through deregulation of the host immune response[13,14]. Besides, VacA can induce radical oxygen species (ROS) production and mitochondrial DNA mutation in gastric epithelial cells.

Another bacterial virulence factor is the *cag* pathogenicity island (cagPAI) which is present in about 60% of *H. pylori* strains and is associated with an increased risk of severe gastritis, ulcer disease and GC[15]. CagA can affect epithelial cells by several mechanisms and may contribute to GC development[16]. CagA was

associated with the epithelial tight-junction scaffolding protein ZO-1 and the transmembrane protein junctional adhesion molecule which modify the composition and function of the apical-junctional complex and disrupt junction-mediated functions[17].

cagPAI also encodes a bacterial type Ⅳ secretion system (T4SS), which translocates CagA into host cells that subsequently affects multiple pathways that alter host cell morphology, signaling and inflammatory responses[17,18]. Once inside the epithelial cell CagA is phosphorylated at tyrosine residues by the epithelial cell c-Src protein and Lyn kinases, and phosphorylated CagA then activates the Src homology-2 domain-containing tyrosine phosphatase, which activates the Erk1/2 pathway, deregulates the phosphatase activity and induces epithelial gastric cell proliferation and transformation[19].

CagA was shown to enhance NF-κB pathway through interaction with TNF-receptor associated factor 6 (TRAF6) and TFG-B-activating kinase-1[20], to activate activator protein-1 (AP-1), PI3K (which leads to B-catenin and NF-κB activation), NFAT and to induce higher levels of interleukin-8 (IL-8)[21,22]. Methylation of MGMT DNA repair gene was also associated with CagA in chronic gastritis, suggesting its role in epigenetic regulation[23]. Other effects of CagA involve interference with proteasome-mediated degradation of the tumor suppressor RUNX3 and TP53[24].

These bacterial factors contribute to adherence, persistence, host immune modulation and virulence. MiRNAs are host factors that may contribute to influence GC risk as each miRNA can potentially control hundreds to thousands of target genes and miRNA deregulation was associated with immune and inflammatory disorders and various malignancies. *H. pylori* have been demonstrated to modulate expression of miRNAs which may further contribute to *H. pylori*-related diseases[14]. However, the true role of miRNA deregulation in the tumorigenesis is not perfectly clear.

In this review we aim to summarize the available evidence concerning the role of microRNAs in gastric carcinogenesis through *H. pylori* infection, inflammation, DNA methylation and progression of preneoplastic conditions.

H. PYLORI, IMMUNE HOST RESPONSES AND INFLAMMATION

Inflammation has long been recognized as a key factor in the development of many types of cancers. *H. pylori* induce chronic gastric inflammation which is the strongest known risk factor for development of atrophic gastritis, metaplasia, dysplasia, and ultimately GC through the accumulation of mutations, epigenetic modifications and deregulation of cell function. The chronic nature of *H. pylori*-gastritis is critical to the carcinogenic potential of this infection, resulting in a long-term interaction between the bacteria, inflammatory mediators and gastric epithelial and stem cells. Indeed, the preneoplastic gastric epithelial changes have been shown to carry numerous genomic, epigenetic and functional abnormalities than can also be detected in cancer tissues[25-28].

Host defense against pathogens requires appropriate innate immune responses, as excessive or inappropriate activation of the immune system can be deleterious. *H. pylori* infection elicits both humoral and cellular immune responses[29]. Host cells recognize invading pathogens and/or their secreted effectors/pathogen associated molecular patterns (PAMPs) through pathogen recognition molecules known as Toll-like receptors (TLRs) and NOD-like receptors, located on the cell membrane and in the cytoplasm, respectively, which subsequently activate adaptor proteins and transcription factors such as the NF-κB and AP-1[30].

Gastric epithelial cells constitute the first line of defense against *H. pylori*. In these cells, the innate immune response is characterized by NOD1-dependent activation of the NF-κB pathway in response to *H. pylori* peptidoglycan which is injected into the host cell cytoplasm *via* the T4SS[31]. NF-κB activation promotes cellular signaling changes and activation of adaptor proteins and transcription factors which mediate the release of cytokines that promote the recruitment of polynuclear cells and the activation of macrophages, dendritic cells (DCs) and mucosa infiltrating lymphocytes which take part in the innate and adaptive immune responses to the bacteria.

The bacteria also interacts with DCs, either in the gut lumen (where mucosal DCs insert dendrites through the tight junctions of the epithelial barrier) or within Peyer's patches in the small intestine (where resident DCs phagocytose bacteria), which may direct the nature of the adaptive immune responses[32]. Myeloid cells (monocyte/macrophage and DCs) constitute the second line of defense, sensing *H. pylori* components *via* TLR2, TLR4, TLR5 or NOD1 signaling. TLRs in the cell membrane of DCs trigger a signaling cascade in the host cell responsible for the initiation of the immune host response and lead to the secretion of proinflammatory cytokines such as IL-1B, IL-6, and TNF-α in order to establish T and B lymphocyte-mediated adaptive immunity[24,33,34]. Indeed, TNF-α contributes to monocyte maturation, IL-6 supports the transition between the early stages of the infection and the sustained mononuclear influx into the infected gastric mucosa, and IL-1B contributes to NF-κB pathway activation in myeloid cells[35].

NF-κB can be activated by *H. pylori* through proinflammatory mediators (*e.g.*, cytokines) and through TLR activation by PAMPs[20]. It has been proposed that *H. pylori* peptidoglycan (injected in the gastric epithelial cell *via* T4SS) activates NF-κB *via* NOD1, which then activates MAPKs in both the NF-κB and AP1 pathways, inducing NF-κB activity and leading to cytokine release namely IL-8[31,36,37]. In macrophages and DCs, the TLR family members TLR2, TLR5, TLR4 and TLR9

are involved in response to *H. pylori* infection[34], but discussion is ongoing as wether *H. pylori* LPS signals *via* TLR4 (a common receptor for Gram-negative enterobacterial LPS) or *via* TLR2 (the main receptor for G+ bacteria lipoteichoic acid), because *H. pylori* LPS lacks distinct features of the prototypical LPS[38]. When activated by bacterial LPS, TLR4 may recruit MyD88 and IRAK which subsequently activates NF-κB[39].

DCs also stimulate the production of IL-17 by lymphoid cells and release IL-23, a major cytokine involved in the induction and maintenance of Th17 responses, leading to a Th17 response against *H. pylori* which can affect the development of *H. pylori* gastritis[34,40,41]. Infection with cagPAI+ strains was associated with an increased production of IL-23[35]. However, an imbalance of the Th17/Treg axis may lead to suppressed Th17 and ineffective bacterial eradication, suggesting that DCs may also play a role in *H. pylori* immune escape through directing a Treg-skewed DC-induced helper T-cell differentiation[42].

Altogether, the mediators released by epithelial cells, macrophages and DCs activate T-lymphocytes with a predominant Th1 response, regulatory T-lymphocytes (Treg), B-lymphocytes which mature into mucosal plasma cells, and neutrophils which actively phagocytize *H. pylori*[24].

Despite the strong immune response, *H. pylori* is not cleared and produces a chronic inflammatory status which requires evasion from the immune system. Although *H. pylori* is generally considered an extracellular microorganism, some evidence supports that at least a subset of *H. pylori* has an intraepithelial location and that a minor fraction of *H. pylori* resides inside gastric epithelial cells, which may represent the site of residence for persistent infection[43]. Autophagy is suggested as an immune innate response against *H. pylori*, decreasing its survival, and it was shown that *H. pylori* can induce autophagy in gastric epithelial cells despite still being capable to replicate in these cells[44,45].

The progressive damage of gastric glands leads to mucosal atrophy and intestinal metaplasia which constitutes an environment with increased risk for the development of dysplasia and cancer. Mucosal atrophy in the gastric body and fundus lead to hypochlorhydria, which may further contribute to the overgrowth of other bacteria that can convert nitrites to carcinogenic nitroso-N-compounds and thus increase the carcinogenic activity in the gastric mucosa[46].

Gastrokine-1 (GKN1) is a protein present in gastric mucosal cells that protects the antral mucosa and promotes healing by facilitating restitution and proliferation after injury and may also play an important role in mucosal inflammation since its expression suppresses activation of NF-κB by inhibiting the degradation and phosphorylation of IkB and inactivating IKKalfa/beta[47,48]. Decreased GKN1 expression has been reported in *H. pylori*-infected patients and it was demonstrated a progressive decrease from chronic gastritis to atrophy and intestinal metaplasia[49]. Remarkably, in the latter study GKN1 was undetectable in tumoral tissues and was expressed in non-tumoral tissues, suggesting that GKN1 plays an important role in mucosal defense, and that its gene acts as a tumor suppressor[50]. More recently, Yoon *et al*[51] demonstrated that CagA reduces GKN1 expression and that GKN1 transfection suppresses the carcinogenic effects of CagA. GKN1 may also influence cytokine production, NF-κB pathway and COX-2 expression[52].

Inflammation and carcinogenesis

Chronic inflammation plays an important role in the development of various cancers, including gastric adenocarcinoma, hepatocellular carcinoma associated with hepatitis B and C, immunoproliferative small intestinal disease associated with Campylobacter jejuni and cancer associated with ulcerative colitis. In fact, up to 25% of all cancers are thought to be associated with chronic inflammation, regardless of the presence or absence of infection[53].

The inflammatory milieu caused by chronic *H. pylori* infection contributes to carcinogenesis through activation of downstream targets that regulate cell cycle progression, proliferation, and apoptosis. NF-κB is a key regulator of inflammation and other cellular cascades and was identified as a molecular bridge between inflammation and cancer, since improper NF-κB activation transactivates several target genes harboring inflammatory (*e.g.,* COX2, iNOS, TNF-α), anti-apoptotic [*e.g.,* cIAP1 and 2, x-linked inhibitor of apoptosis (XIAP), Bcl-2, Bcl-3, Bcl-xL], cell cycle regulatory (*e.g.,* cyclin D1) and proangiogenic (*e.g.,* VEGF, angiopoietin) functions, and/or down-regulates pro-apoptotic genes (*e.g.,* p53, Bax, Bad)[54].

Other inflammatory mediators released from epithelial, mesenchymal and immune cells like proinflammatory cytokines, growth factors, ROS and reactive nitrogen species (RNS) can also promote cell proliferation, migration, angiogenesis and invasion through a stepwise accumulation of genetic and epigenetic alterations. Among these, cytokines play key roles in the inflammatory process, and IL-1B, IL-6, and TNF-α have been implicated in cancer development. Interleukin-1B and TNF-α induce NF-κB activation, which promotes cell growth/proliferation, suppresses apoptosis of epithelial cells and stimulates the production of growth factors and cytokines such as epidermal growth factor, IL-6, COX2 and ROS[55]. IL-6 activates STAT3 (signal transducer and activator of transcription 3), enhancing cell growth and growth factor production[56]. Besides, IL-6 promotes COX-2 induction and increases ROS production[57]. COX-2 subsequently enhances cell growth and angiogenesis while ROS can modify protein function[24].

TLRs may also lead to the production of inflammatory cytokines through AP-1 and NF-κB dependent transcription, playing a role in carcinogenesis through the activation of NF-κB and COX2[58-60]. In fact, incr-

easing levels of TLR2, 4 and 5 and decreasing levels of TLR inhibitors (PPARy and TOLLIP) were demonstrated through the spectrum of gastric carcinogenesis in our previous studies, suggesting that increasing TLR expression is associated with the progression of preneoplastic lesions[61,62].

The intricate balance between pro- and anti-inflammatory cytokines in chronic inflammation may mediate the outcome of *H. pylori* infection by affecting cell proliferation and apoptosis and various immune regulators take part in this regulation. An important role for miRNAs in modulating both the innate and adaptive immune responses has been suggested in various studies[63,64]. In the next section we will summarize the evidence regarding the role of miRNAs in the regulation of innate and adaptive immunity and inflammation.

MicroRNAs involved in the host immune response to H. pylori

The first miRNA found to be influenced by *H. pylori* infection was miR-21. miR-21 was found to be over-expressed in both *H. pylori*-infected tissues and in GC[65,66]. NF-κB and IL-6 activate AP-1 and STAT3 respectively which are able to induce miR-21 and could explain miR-21 upregulation during *H. pylori* infection. Matsushima *et al*[11] characterized miRNA expression in *H. pylori*-infected human gastric mucosa and found 30 miRNAs significantly decreased in *H. pylori*-positive patients. Eight miRNAs enabled discrimination of *H. pylori* status with acceptable accuracy - miR-204 was the most decreased miRNA in *H. pylori*-infected followed by miR-455, miR-141, miR-203, let-7f, and miR-200a, whereas miRNA-223 was the only to be significantly increased. Gastritis scores of activity and chronic inflammation according to the updated Sydney system correlated significantly with the expression levels of diverse miRNAs. miR-223 expression was significantly increased in *H. pylori* -infected gastric mucosa and correlated positively with the degree of neutrophil infiltration (activity scores). miR-375 and miR-200c were inversely correlated with chronic inflammation and *H. pylori* density scores, respectively. On the other hand, in this study no significant correlation was found between miRNA expression and the degree of glandular atrophy and intestinal metaplasia. Expression levels of some miRNAs, including let-7 family, were significantly altered following infection with CagA(+) strains but not with CagA(-), suggesting that cagA might be involved in the regulatory processes of some miRNAs.

The differential expression of various miRNAs in *H. pylori*-positive gastric human tissues and *H. pylori* -negative controls was also examined in another study and significant correlations between 17 miRNAs, chronic gastritis and the level of the pro-inflammatory cytokines IL-1B, IL-6, IL-8 and TNF-α were found. However, that correlation disappeared in the presence of gastric atrophy and was inverse, for IL-6 and IL-8, in intestinal metaplasia[67]. Levels of miR-103, miR-375 and miR-200a were negatively correlated with IL-6, IL-8 and TNF-α, respectively. Let-7b was also found to be inversely correlated with IL-1b levels[67].

H. pylori CagA(+) was shown to decrease let-7 expression in the gastric epithelium and let-7 family expression levels have been shown to be negatively associated with histological scores for activity, chronic inflammation and *H. pylori* density[11,68]. Specifically, let-7b was significantly decreased in *H. pylori* -gastritis patients in a CagA-dependent manner and TLR4 3'UTR mRNA was shown to be a target for let-7b and thus let-7b can negatively regulate TLR4 expression post-transcriptionally[69]. Indeed, Teng *et al*[69] demonstrated that let-7b inhibition lead to increased TLR4 protein levels, activation of NF-κB and increased expression of COX-2 and CyclinD1, suggesting that *H. pylori* infection upregulates TLR4 expression and its downstream genes by downregulating let-7b expression. Furthermore, let-7b overexpression was associated with MyD88 downregulation and inhibition of NF-κB activity. Thus, decreased let-7b expression in *H. pylori* infection may promote inflammatory responses that contribute to the progression of gastric preneoplastic conditions. Let-7 was also found participate in cell differentiation, proliferation and apoptosis control and to be downregulated in several cancers including GC, suggesting that it acts as a tumor suppressor miRNA[70]. miR-7 was also found to be significantly decreased in both gastritis and gastric tumors in a mouse model, and in human GC the expression of miR-7 was inversely correlated with the levels of IL-1B and TNF-α, suggesting that miR-7 downregulation is related to the severity of inflammatory responses and possibly linked with gastric tumorigenesis[71]. In this regard, *in vitro* experiments showed that CagA significantly attenuates let-7 expression and enhances c-Myc, DNA methyltransferase 3B (DNMT3B) and Enhancer of Zeste homologue 2 (EZH2) expression, leading to Ras oncoprotein pathway activation with no associated inflammation[72].

miR-451 is also downregulated in both *H. pylori* infection and GC and targets macrophage migration inhibitory factor (MIF) and an inverse correlation was found between miR-451 and MIF expression in GC, suggesting that miR-451 functions as a tumor suppressor by silencing MIF expression, leading to a proliferative and anti-apoptotic phenotype[73].

Early in the acute phase of the infection *H. pylori* induces strong inflammatory responses and a transitory hypochlorhydria through repression of gastric H^+, K^+/ATP-ase which further facilitates gastric *H. pylori* colonization. NF-κB possesses binding regions in the H^{+}/K^{+} promoter and have been shown to repress its transcriptional activity[74]. CagA protein and peptidoglycan-dependent mobilization of NF-κB were also implied in $H^{+}/K^{+}\alpha$ repression. miR-1289 is upregulated in *H. pylori* CagA infection and miR-1289 overexpression was found to attenuate $H^{+}/K^{+}\alpha$ expression through targeting $H^{+}/K^{+}\alpha$ 3' UTR and thus repressing mRNA translation[75].

H. pylori may also deregulate miRNA expression

to evade host defenses and successfully persist in the gastric niche. TLRs on the membrane of monocytes/DCs recognize and bind to PAMPs and then trigger downstream signaling pathways to initiate inflammatory responses. MiRNAs may regulate the tightly controlled TLR signaling and the downstream expression of genes and molecules in order to fine-tune the innate immune response and prevent overwhelming inflammation[76]. miR-146a and miR-155 were found to be upregulated by *H. pylori* (independently of cagPAI status) and may regulate the acute inflammatory response in myeloid cells and/or lymphocytes after pathogen recognition by TLR contributing to a negative regulation of the proinflammatory immune response[35]. TLR signaling activation and inflammatory cytokines such as TNF-α and IL-1B have also been shown to upregulate miR-146 and miR-155 during *H. pylori* infection[77,78].

miR-146 was found to be rapidly upregulated after LPS stimulation and after *H. pylori* infection in a CagA-independent and in a NF-κB-dependent manner through TLR signaling[79-81]. MiR-146a role was further explored and it was found that miR-146a targets and silences the TLR-signaling adaptor molecules interleukin-1 receptor-associated kinase (IRAK1) and TNF receptor-associated factor 6 (TRAF6) resulting in a negative-feedback loop regulation of TLR, NF-κB pathway and the downstream proinflammatory signaling in response to bacterial products, thus avoiding the overproduction of proinflammatory IL-1B and TNF-α cytokines[79-82]. As a result, the expression of key elements of the proinflammatory innate and adaptive immune responses like IL-1B, IL-8, TNF-α, growth related oncogene alpha, and macrophage inflammatory protein is negatively regulated by miR-146a overexpression in *H. pylori* infection[80], suggesting that this single miRNA plays an important role in the control of the inflammatory response to *H. pylori*, possibly restraining the tissue damage observed in patients with gastritis. Additionally, miR-146a overexpression was found to post-transcriptionally decrease prostaglandin endoperoxide synthase 2 expression[83], an enzyme responsible for the production of prostaglandin E2 which has been associated with *H. pylori* infection and infiltration of inflammatory cells to the gastric mucosa[84].

miR-155 is induced during both bacterial and viral infections in myeloid cells through activation of TLR-signaling pathways and also *via* a TLR-independent component that results partly from the activation of MyD88/Trif-independent PAMP receptors by T4SS[77,85]. *H. pylori* was found to upregulate miR-155 expression also *via* a NF-κB- and AP-1-dependent manner and significantly higher miR-155 levels were found in *H. pylori*-positive patients as compared with *H. pylori*-negative controls[86,87]. miR-155 was then found to regulate inflammation by targeting and decreasing myeloid differentiation primary response protein 88 (MyD88) protein levels which subsequently results in decreased NF-κB activation and thus in decreased release of proinflammatory cytokines like IL-8 and GRO-a, suggesting that miR-155 overexpression during *H. pylori* infection is also involved in the negative feedback regulation of the host inflammatory response through attenuating NF-κB activity[86,87]. Ceppi *et al*[88] showed that miR-155 modulates the TLR/IL-1 signaling pathway by targeting TAB2, an important signaling molecule that facilitates the activation of TRAF6 and NF-κB. Other gene transcripts of the NF-κB pathway like KK-epsilon (IKK), SMAD2 and Fas-associated Death Domains (FADD) were also described as miR-155 targets in one study[86].

Besides this role in the negative feedback regulation of the immune host response to *H. pylori*, miR-155 seems to be important in adaptive immunity contributing to the development of regulatory T cells (Treg), Th17 differentiation, induction of IL-17 and thus to the control of *H. pylori* infection.

H. pylori infection results in a predominantly T-cell mediated immunity rather than humoral immunity, with Th1 and Th17 responses which increase the production of IL-1B, TNF-α and IL-8[64]. Th17 cell differentiation is promoted by TNF-α and IL-6 while Th1 responses are triggered by IL-12 and INF-gamma[89]. MiR-155 deficient mice showed decreased production of IFN-γ and IL-17, impaired pathogen-specific Th1 and Th17 responses and fail to control *H. pylori* infection suggesting that miR-155 expression is required for the Th17/Th1 differentiation[90]. Interestingly, miR-155 deficient mice developed less severe infection-induced immunopathology such as severe chronic atrophic gastritis, epithelial hyperplasia and intestinal metaplasia.

Cholera toxin B subunit (CTB-UE), a multi-epitope vaccine composed by the cholera toxin B subunit and copies of B and Th cell epitopes from *H. pylori* urease A and B, showed a good therapeutic effect on *H. pylori* infection in a mice model which was closely related to the immune response mediated by miR-155 upregulation[91]. Indeed, CTB-UE vaccination significantly upregulated miR-155 expression which was associated with the induction of an immune response biased towards Th1 cells. In this experiment, miR-155 overexpression was also associated with decreased IL-17 production, maybe by inhibition of Th17 response, suggesting that CTB-UE could relieve *H. pylori* induced gastric inflammatory reaction *via* miR-155 upregulation[92].

Tang *et al*[93] found that autophagy is decreased in patients with chronic *H. pylori* infection and that miR-30b is upregulated during *H. pylori* infection. In their experiment mir-30b expression compromised autophagy and increased bacterial survival and replication through targeting BECN1 and ATG12, although there were inconsistent results concerning autophagy between *in vivo* and *in vitro* infections, suggesting that *H. pylori*-mediated autophagic processes may be complex and that many factors *in vivo* may be involved in autophagy inhibition[93].

Together these data suggest that *H. pylori* deregulates host miRNA expression to manipulate the host inflammatory immune response, which may promote bacterial survival and persistence within the gastric

mucosa. Besides, as these miRNAs have established roles in carcinogenesis as well as innate immunity, they could serve as an important link between *H. pylori*-induced inflammation and carcinogenesis. The previous findings suggest that microRNAs play an important role in the fine-tuning of both innate and adaptive immune responses and that miRNA deregulation may contribute to both *H. pylori* persistence and to *H. pylori* -mediated pathology.

MICRORNAS AND DNA METHYLATION - THE BRIDGE BETWEEN INFLAMMATION AND CANCER?

Gastric carcinogenesis involves gradual accumulation of various genetic and epigenetic alterations leading to oncogene activation and loss of tumor suppressor gene function. Genetic alterations, such as p53, KRAS, PIK3CA and MLL mutations, as well as PIK3CA, C-MET, ERBB4 and CD44 amplifications are frequently found in GC, suggesting that may be key tumorigenic events[94].

In cancers arising in inflammatory environments, mutagenesis and epigenetic deregulation are the main mechanisms driving epithelial cells in the direction of cancer. Increased mutation burden of the epithelial genome occurs through both the increased occurrence of mutations due to direct damage of DNA (*e.g.,* ROS, RNS) and deficient repair of mutations prior to DNA replication (reduced function of MGM and MMR genes). *H. pylori* infection leads to chronic inflammation, accumulation of ROS and oxidative DNA damage in the gastric mucosa and was also associated with methylation and silencing of a number of genes through aberrant DNA methylation in the gastric mucosa, which may contribute to gastric carcinogenesis through the silencing of tumor suppressor genes[95-97]. Indeed, several inflammatory mediators, such as TNF-α, IL-1B and ROS were implicated in aberrant DNA methylation during gastric carcinogenesis and a growing body of evidence suggests that, in addition to genetic alterations, epigenetic changes are also involved in the initiation and progression of GC[24,98,99]. Aberrant methylation of promoter CpG islands was also demonstrated in non-neoplastic tissues with *H. pylori* gastritis and CpG methylation has been shown to be partially reversible after *H. pylori* eradication further supporting the role of *H. pylori* and inflammatory mediators in epigenetic regulation[23,27,100,101].

Therefore, DNA methylation seems to be an important epigenetic process that occurs during malignant transformation and the rate of gene methylation is considered to be correlated with an increased risk of GC[102,103]. DNA methylation is regulated by a family of DNMT and includes global hypermethylation and hypermethylation of CpG islands confined to the regulatory regions of human genes. Methylation of CpG islands in promoter regions causes silencing of the downstream gene, whereas methylation in the coding region is usually associated with increased gene transcription. Thus, cancers display regional hypermethylation of promoter regions and global hypomethylation. The extensive epigenetic alteration in the background mucosa that gives rise to dysplasia and cancers represents an epigenetic field defect in inflammation and infection associated cancers. CpG methylation occurs early in gastric carcinogenesis, affecting genes such as MLH1, p14, p15, p16, CDKN2A, CDH1 - E-cadherin, LOX, APC, RUNX3, thrombospondin-1, tissue inhibitor of metalloproteinase 3, COX-2, and MGMT[26,96,98,104,105].

Several reports describe that binding of transcription factors to the promoter regions of specific miRNA genes activate the transcription of pre-miRNAs, thus increasing the expression of mature miRNAs. As an example, increased expression of c-Myc leads to the activation of miR-17-92 cluster by binding to its regulatory region[106]. On the other hand, intronic miRNAs are coordinately expressed with their host gene mRNA, while some miRNAs are located at cancer-associated genomic regions frequently involved in chromosomal abnormalities that may affect the differential expression of miRNAs. DNA methylation and histone modification, epigenetic changes that play critical roles in chromatin remodeling and regulation of gene expression may also influence the expression of some miRNAs genes by epigenetic alterations in their promoter regions. *H. pylori* infection was found to lead to ubiquitination and reduction of Drosha protein levels in GC cells and treatment of GC cells with a proteasome inhibitor (MG132) was associated with preservation of Drosha protein levels despite *H. pylori* infection, suggesting that *H. pylori* infection enhances the ubiquitin-proteasome pathway and may lead to downregulation of miRNAs by influencing Drosha expression post-transcriptionally[107].

Several tumor-suppressor miRNAs, including miR-124a, miR-137, miR-193a and miR-127 were reported to be silenced by aberrant DNA methylation of their promoter CpG islands in cancers[96]. *H. pylori* long-term colonization may induce epigenetic modification of gastric mucosal genes, including on the promoter regions of tumor suppressor miRNAs, which cannot be completely reversed only by bacterial eradication and thus miRNA silencing by aberrant DNA methylation is probably involved in gastric carcinogenesis[108]. Indeed, several miRNAs such as miR-210, miR-375 and miR-124-a1/a2/a3 were shown to have reduced expression in the gastric epithelium of chronically *H. pylori* -infected gastric mucosa due to DNA methylation[96,109]. Epigenetic silencing of let-7 with subsequent Ras pathway activation was also demonstrated after CagA transfection through enhancement of c-myc and DNMT3B and attenuation of miR-6a and miR-101 expression[110].

Higher levels of miRNA gene methylation were also found in noncancerous gastric mucosa of GC patients as compared with *H. pylori*-negative mucosa, suggesting that miRNA silencing is involved in the formation of a field defect for GC[96]. miR-124a (downregulated in *H. pylori*-infection) was found to down-regulate CDK6, an

Table 1 MicroRNAs reduced by DNA methylation in *Helicobacter pylori* infection

MicroRNA	Targets	Consequences/associations
miR-210	STMN1	Aberrant proliferation
	DIMT1	Increased *H. pylori* content, atrophy and neutrophil and mononuclear infiltration
miR-375	MDM2	p53 inhibition
	JAK1/STAT3	JAK1/STAT3 activation and neoplastic transformation
	14-3-3	Bcl binding and cell survival
	PDK1	PI3K/Akt pathway
miR-124	CDK6	Cell cycle progression
Let-7a	c-myc and DNMT3B	Ras pathway activation
miR-34	Bcl-2	Apoptosis inhibition
miR-10b	MAPs	Microtubule-associated protein oncogene
miR-185	DNMT1 and EZH2	Proliferation and EMT
		LNM and poorer prognosis
miR-490-3p	Cyclin B1	EMT; proliferation; colony formation; migration; invasion
	SMARCD1	Metastasis and poorer survival
		Decreased through the spectrum of gastric carcinogenesis

STMN1: Stathmin/oncoprotein 18; DIMT1: DIM1 dimethyladenosine transferase 1 homolog (*S. cerevesiae*); MDM2: Mouse double minute 2 homolog/E3 ubiquitin-protein ligase Mdm2; JAK1: Janus kinase 1; STAT3: Signal transducer and activator of transcription 3; PDK1: Phosphoinositide-dependent kinase-1; CDK6: Cyclin-dependent kinase 6; DNMT3B: DNA (cytosine-5-)-methyltransferase 3 beta; Bcl-2: B-cell lymphoma 2; MAPs: Microtubule-associated proteins; DNMT1: DNA (cytosine-5)-methyltransferase 1; EZH2: Enhancer of zeste homolog 2; EMT: Epithelial-mesenchymal transition; LNM: Lymph node metastasis; SMARCD1: SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily D member 1.

oncogene involved in cell cycle progression, suggesting that miR-124a is involved in gastric carcinogenesis[111]. miR-34b and miR-34c (tumor suppressor miRNAs) and miR-10b (a miRNA that targets the microtubule-associated protein oncogene) were also found to be epigenetically silenced in GC due to hypermethylation of the neighboring CpG islands[112,113]. In the latter study, treatment with demethylating agents decreased miR-10b methylation and restored its expression, suggesting that modulation of miR-10b may represent a therapeutic approach for treating GC[113].

CpG island hypermethylation was also associated with decreased miR-210 in *H. pylori* -positive gastric mucosa, and miR-210 downregulation was associated with STMN1 upregulation, possibly leading to aberrant proliferation of gastric epithelial cells during chronic *H. pylori* infection[109]. In this study, miR-210 decreased in parallel with increased grades of neutrophil and mononuclear cell infiltration, atrophy and *H. pylori* content suggesting that miR-210 methylation is associated with disease progression of *H. pylori*-mediated gastric lesions. Besides, decreased miR-210 levels were lower in tumor tissues than in normal mucosa and 10 oncogenes were found to be strongly suppressed by miR-210, namely STMN1 (oncoprotein 18) and demethyladenosine transferase-1 (DIMT1). STMN1 and DIMT1 upregulation was also demonstrated in *H. pylori*-positive human stomachs.

GKN1 is thought to function as an hypomethylating agent and to exert its antiproliferative effects through downregulation of DNMT1 and EZH2, a histone methyltransferase involved in proliferation and epithelial-mesenchymal transition (EMT) promotion (by interacting with Snail and suppressing E-cadherin expression)[50,52,114]. Indeed, inactivation of DNMT1 and EZH2 in GC cells suppressed cell growth through G0/G1 and G2/M cell-cycle arrest, suggesting that GKN1 acts as a tumor suppressor through the regulation of epigenetic regulatory components and EMT-related proteins. Interestingly, expression of DNMT1 and c-myc was also positively associated with *H. pylori* CagA protein and methylation status, strongly supporting the view that GKN1 may play an important role in epigenetic regulation[115]. GKN1 was also found to upregulate miR-185 and was positively correlated with miR-185 expression and inversely correlated with DNMT1 and EZH2 expression. DNMT1 and EZH2 were found as targets of miR-185, suggesting that miR-185 inhibits cell growth by inducing cell-cycle arrest through the inactivation of DNMT1 and EZH2[114]. Accordingly, miR-185 downregulation was demonstrated in GC and lower miR-185 levels were associated with lymph node metastasis (LNM) and poorer prognosis[116].

The above results highlight the role of DNA methylation as a mechanism for epigenetic silencing of miRNA genes during chronic inflammation. Table 1 summarizes the microRNAs that were found to be reduced by DNA methylation in *H. pylori* infection and its target genes. Since aberrant DNA methylation has also been reported in other chronic inflammatory diseases that are causative for cancers, it seems that similar inflammation-induced DNA methylation leading to miRNA gene silencing can be an underlying tumorigenic mechanism associated with GC.

GASTRIC PRENEOPLASTIC CONDITIONS AND GASTRIC CARCINOGENESIS - THE ROLE OF MICRORNAS

From the early stages of *H. pylori* gastritis, the infection and associated inflammation lead to epithelial cell

mutations, epigenetic, microRNA and gene expression changes, genomic instability, altered cellular signaling, and imbalance of proliferation and apoptosis of gastric epithelial cells, driving the progression from gastritis to pre-neoplastic and neoplastic lesions[26]. Shiotani *et al*[117] found a higher expression of oncogenic miRNAs (miR-17/92, miR-106b-93-25, miR-21, miR-194 and miR-196) in metaplastic intestinal mucosa compared with non-intestinal metaplastic mucosa and that *H. pylori* eradication improves miRNA deregulation in the gastric mucosa but not in metaplastic glands, suggesting that *H. pylori* long-term colonization induces epigenetic modifications not completely reversible by *H. pylori* eradication alone. Wang *et al*[118] also analyzed miRNA expression patterns in *H. pylori*-related gastritis and gastric intestinal metaplasia and found 20 differentially expressed miRNAs (DEMs), including 12 up-regulated and 8 down-regulated, and the top 5 DEMs were miR-486p, miR-645, miR-624, miR-504, and hsa-miR-106b. Lower expression of miR-106b and miR-204 was also found in *H. pylori*-positive gastric mucosa, suggesting that the downregulation of these miRNAs is associated with *H. pylori*-related chronic gastritis[11].

miR-106b was implicated in TGF-β and MAPK signaling pathways and miR-204 was related with calcium and neurotrophic signaling pathways and axon guidance[118]. In another study miR-204 was linked to the down-regulation of sirtuin 1 (SIRT1) and to the reversion of SIRT1-induced EMT and invasion in GC cells[119]. miR-106b was associated with suppression of TGF-β-induced cell cycle arrest and promotion of GC development in a previous study[120]. The frequency and extent of miR-106a (a miRNA overexpressed in GC) expression gradually increased during the transition from atypical hyperplasia to advanced carcinoma and had already positive signals in early precancerous lesions but negative signals in normal gastric mucosal epithelial cells, suggesting that the early changes of miR-106a potentially can become biomarkers for the early detection of GC[121]. miR-106a is upregulated in GC and targets retinoblastoma protein (RB1), a tumor suppressor protein that inhibits transcription factors of the E2F family[65]. miR-106a, upregulated in GC, was correlated with lymphatic and distant metastasis[65,122].

miR-320, a tumor suppressor miRNA downregulated in various solid tumors, targets Mcl-1 anti-apoptotic factor expression and miR-320 downregulation by *H. pylori* was demonstrated in a CagA-dependent manner. Furthermore, Mcl-1 expression levels were found to increase in parallel with the severity of neoplastic lesions (nonatrophic gastritis, intestinal metaplasia, or adenocarcinoma), Mcl-1 overexpression was associated with chemotherapeutic resistance and relapse of tumors and Mcl-1 depletion was found to promote apoptosis in cancer cells[123]. These findings suggest that *H. pylori* CagA suppresses miR-320 and upregulates Mcl-1 leading to inhibition of apoptosis and increasing the risk for GC. miR-101 and miR-515-5p are also downregulated in *H. pylori*-positive tissues and in GC and their downregulation was associated with an anti-apoptotic phenotype by targeting Mcl-1, leading to Mcl-1 overexpression[11,108,124]. Recently, Zhou *et al*[124] found that miR-101 also strongly reduces the expression of SOCS2 oncogene in GC cells and that miR-101 levels were inversely correlated with SOCS2 expression, suggesting that miR-101 acts as a growth-suppressive miRNA in *H. pylori*-related GC. CagA also attenuated miR-101 expression, which in turn further attenuated let-7 expression by histone and DNA methylation[72].

Another miRNA implicated in the progression of gastric preneoplastic conditions is miR-490-3p whose expression is progressively downregulated in gastritis, intestinal metaplasia and adenocarcinoma during *H. pylori* infection[125]. Hypermethylation of the promoter region of miR-490-3p was demonstrated in human GC tissues as well as miR-490-3p growth and metastasis suppressive effects (inducing G2/M and intra-S phase arrest and downregulating cyclin B1) through directly targeting SMARCD1 (a SWI/SNF chromatin remodelling complex subunit). Indeed, SMARCD1 was found to be markedly upregulated in GC and its higher expression was associated with poorer patients' survival independent of TNM staging. These findings suggest that *H. pylori* silences miR-490-3p expression by hypermethylation, which subsequently activates SMARCD1 conferring malignant phenotypes, mechanistically linking *H. pylori*, chromatin remodeling and gastric carcinogenesis[125]. It was also shown that miR-490-3p upregulates epithelial markers (*i.e.,* syndecan-1 and zo-1), downregulates mesenchymal markers (*i.e.,* fibronectin and vimentin) and inhibits colony formation, growth, cell migration and invasiveness, supporting the role of this miRNA in inhibiting EMT.

Forkhead box M1 (FoxM1), a key positive cell-cycle regulator is also implied in the pathogenesis of several types of cancers and was found to be increasingly overexpressed through the spectrum of gastric carcinogenesis. Feng *et al*[126] showed that mRNA expression of FoxM1 gradually increased from gastritis to cancer as compared with noncancerous tissues (6.7% of the cells in noncancerous gastric tissues, 21.7% in gastritis, 36.4% in AG/IM and 89.2% in GC). *H. pylori* CagA(+) infection was shown to reduce $P27^{Kip1}$ expression (a tumor suppressor which negative regulates cell-cycle) and was associated with FoxM1 upregulation and increased cell proliferation, alterations partially reversed by knockdown of FoxM1, suggesting that FoxM1 mediates the inhibition of $P27^{Kip1}$ induced by *H. pylori*. miR-370 directly targets FoxM1 gene reducing FoxM1 activity. Accordingly, expression of miR-370 gradually decreased from superficial gastritis, atrophic gastritis/IM to GC samples. Together these findings suggest that the miR-370-FoxM1 pathway is involved in the progression of *H. pylori*-induced gastritis to GC by affecting $P27^{Kip1}$ expression. The FoxM1 overexpression may reduce $P27^{Kip1}$ and thus increase cell proliferation and promotion of gastric carcinogenesis. Furthermore, transcription of

$P27^{Kip1}$ was inhibited by CagA *via* PI3K/Akt pathway in another study[127]. However, Lo *et al*[128] found that miR-370 was overexpressed in GC tissues and in plasma of GC patients and higher miR-370 levels were associated with LNM and higher clinical stage. TGF-β receptor Ⅱ was identified as a target for miR-370 in this study and an inverse correlation was found between mir-370 and TFG-B-RII in GC tissues.

miR-584 and miR-1290 upregulation was also demonstrated after CagA transfection, with subsequent downregulation of Foxa1 expression and promotion of EMT *in vitro*[110]. It was also shown that mice over-expressing miR-584 and miR-1290 developed gastric intestinal metaplasia after a long follow-up, suggesting a role for these miRNAs in the progression of preneoplastic conditions induced by *H. pylori*.

GKN1, a protein involved in mucosal defense and in the regulation of inflammatory pathways, was found to be decreased in *H. pylori*-infected mucosa and a progressive decrease from chronic gastritis to atrophy and intestinal metaplasia was demonstrated[49,50]. In non-neoplastic mucosal samples of patients with sporadic GC, GKN1 levels were able to predict gastric mucosal atrophy and intestinal metaplasia risk with an AUC value of 0.865 and 0.973, respectively, implicating GKN1 as an important player in gastric mucosal inflammation and a marker of the progression of gastric carcinogenesis[115]. GKN1 was found to upregulate miR-185 which targets DNMT1 and EZH2 expression and thus reduces DNA methylation.

Finally, the existence of various metaplastic processes has been recognized, including goblet cell intestinal metaplasia and spasmolytic-polypeptide-expressing metaplasia (SPEM)[129,130]. CD44 is a major adhesion molecule and receptor for hyaluronic acid that can coordinate normal and metaplastic gastric epithelial progenitor cell proliferation under conditions of parietal cell loss and is a putative gastric stem cell marker[131]. CD44v, a variant of CD44, was shown to interact with xCT (a glutamate-cystine transporter) and to contribute to ROS defense in cancer cells[132]. Inflammatory response to *H. pylori* infection leads to increased expression of CD44 and CD44v9 in the gastric mucosa; CD44v9 was found to be overexpressed in SPEM in mice models and CD44 ablation significantly attenuated SPEM development by suppressing the proliferation of metaplastic cells at the base of their gastric glands[133]. Ishimoto *et al*[134] recently showed that CD44v9 expression in gastric mucosal cells is correlated with *H. pylori* infection and that there is an association between CD44v9 expression in the gastric mucosa adjacent to tumor and in tumor cells, suggesting that the development of GC CD44v9+ is associated with *de novo* expression in the mucosa adjacent to the tumor. It was shown that *H. pylori* infection is associated with increasing number of myeloperoxidase inflammatory cells in the gastric mucosa leading to ROS accumulation which can induce miR-328-mediated CD44 overexpression, suggesting a role for miR-328 in *de novo* expression of CD44[134]. The authors concluded that CD44v expression was regulated by miR-328 suppression and it is possible that CD44v promotes the survival and proliferation of metaplastic cells which give rise to SPEM.

In vitro studies have also shown that miR-296-5p attenuates CDX1 anti-growth effects partly through ERK1/2 activation[135]. Indeed, GC tissues presented loss of CDX1 when compared with adjacent IM tissues and miR-296-5p was inversely correlated with CDX1, suggesting that the miR-296-5p-CDX1-ERK1/2 may be important to the progression of IM to GC and may provide therapeutic targets for the treatment of GC[135].

H. PYLORI RELATED MICRORNAS AND EMT, CELL-CYCLE AND APOPTOSIS

The deregulation of cell cycle progression and increased cellular proliferation are hallmarks of malignancies. Cell cycle progression requires coordinated expression of cyclins, which results in sequential activation of cyclin-dependent kinases (CDKs). miRNA deregulation can promote cell cycle progression by upregulating cyclin expression and/or down-regulating CDK inhibitors expression (p15, 16, 18, 19, 21, 27, 28, 57)[14]. *H. pylori* may possibly exert its carcinogenic effects partly by modulating cyclins, CDKs and CDK inhibitors and deregulation of host miRNAs may affect the regulation of cell cycle and increase the propensity for gastric transformation[136].

Cellular transformation is also characterized by increased cellular proliferation and evasion of apoptosis. Apoptosis can be dependent on either the intrinsic or extrinsic pathways. Extrinsic apoptosis pathway is initiated through the activation of pro-apoptotic death receptors located in the cell surface by ligands like TNF. Ligand binding induces receptor clustering and the recruitment of the adaptor protein FADD, leading to induction of caspases and ultimately cell-death. The intrinsic apoptosis pathway is initiated within cells and hinges on the balance between pro-apoptotic (*e.g.,* Bax, Bak, Bim, BNIP3L, and Bid) and anti-apoptotic (*e.g.,* Bcl-2, Bcl-xL, and Mcl-1) proteins. MicroRNAs seem to play a role in apoptosis regulation by altering the expression of pro-apoptotic and anti-apoptotic factors.

A large number of microRNAs have been associated with the development and progression of GC, some being indicated as potential biomarkers for early diagnosis in patients at risk and others implicated as prognostic factors. In this review we summarize the evidence about microRNAs associated with both *H. pylori* and GC cancer, as recent reviews focused on the topic of microRNAs and GC in general.

The pro-inflammatory miR-21 was found to be overexpressed in *H. pylori* infection and was associated with decreased apoptosis, increased proliferation and invasion, suggesting that miR-21 may be important in the development of GC[66]. Indeed, miR-21 was found to negatively regulate RECK, a tumor suppressor gene

and suppressor of metastasis and angiogenesis that modulates matrix metalloproteases (MMPs) and is decreased in GC samples. Other tumor suppressors have been identified as miR-21 targets, such as PTEN (phosphatase and tensin homolog - a negative regulator of the Pi3K/Akt signaling pathway)[137,138] and actin-binding protein[139]. miR-222 is also upregulated in *H. pylori*-infected gastric mucosa and GC, and ectopic expression of miR-222 was found to promote cell proliferation and colony formation[140]. RECK was identified as a target for miR-222 and an inverse correlation between miR-222 levels and RECK was found suggesting that *H. pylori* may function as an initiator in carcinogenesis by upregulating miR-222, leading to RECK inhibition and thus promoting proliferation[140].

MiR-146a is involved in the regulation of innate immunity and inflammatory response to *H. pylori*, acting as a controller of the inflammatory response through the modulation of TLRs and cytokine signaling pathways and by reducing NF-κB activity through negative regulation of IRAK1 and TRAF6[79,80]. It is also well established that TLR2, 4, 5 and 9 are involved in *H. pylori* recognition[62,141] and that NF-κB is a key molecule in inflammation-cancer link[142]. miR-146a upregulation was found in *H. pylori*-positive gastric mucosa and in GC tissues as compared with matched non-tumor adjacent tissues[143]. In this study miR-146a was found to inhibit apoptosis by decreasing levels of SMAD4 (SMAD family member 4 - identified as a direct target of miR-146a), suggesting that miR-146a plays a role in the development of GC. Another study also found miR-146a upregulation in a GC mice model but identified caspase recruitment domain-containing protein 10 (CARD10) and COP9 signalosome complex subunit 8 (COPS8) as miR-146a targets. CARD10 and COPS8 were found to be involved in NF-κB activation, suggesting that miR-146a inhibits NF-κB activation thus reducing the expression of NF-κB -regulated tumor-promoting cytokines and growth factors and suggesting that in fact miR-146a have tumor suppressing properties[144]. Further supporting that miR-146a acts as a tumor suppressor, Hou *et al*[145] found decreased expression of miR-146a in 84% (36/43) of GC tissue samples and lower miR-146a expression was significantly associated with increased tumor size, poor differentiation and poorer overall survival. In fact, in these study miR-146a inhibited cell proliferation and promoted apoptosis in GC cell lines[145]. Accordingly, miR-146a was associated with suppression of invasion and metastasis in GC cells and in a mice model through targeting L1 cell adhesion molecule[146]. Lower expression levels of miR-146a were also found in GC tissues as compared with corresponding noncancerous tissue, and lower miR-146a levels were significantly associated with LNM, venous invasion and poorer overall survival[147]. Inhibition of migration and invasion through downregulation of EGFR and IRAK1 expression were attributed to miR-146 in the previous study. Pro-apoptotic effects of miR-146a through COX-2 inhibition were also shown in human GC cells and miR-146a density was positively correlated with apoptosis rates in *H. pylori*-positive GC tissues and negatively correlated with LNM among *H. pylori*-positive GC patients[148]. The previous findings were confirmed in a recent miRNA PCR array where it was found that miR-146a-5p is downregulated in GC patients, and low-expression of mir-124-3p, mir-146a-5p, mir-155-5p and mir-335-5p was significantly associated with LNM, lymphatic invasion, venous invasion and poor differentiation[149]. In a different study miR-155 was found to target SMAD2 and FADD, reducing their expression and leading to the downregulation of caspases and inhibition of apoptosis, thus suggesting an oncogenic potential for this microRNA[86].

In addition to microbial and environmental factors, there are a number of host factors that may contribute to gastric carcinogenesis namely single-nucleotide polymorphisms (SNPs) in inflammation-related miRNA, since only a small proportion of infected patients ultimately develop GC. Some studies have demonstrated that rs2910164 SNPs in miR-146a precursor can reduce mature miR-146a production which may modify the inflammatory process and miR-146a SNPs are the most extensively studied polymorphisms regarding increased susceptibility to GC[150,151]. However, some inconsistencies were found in the literature. Indeed, Okubo *et al*[152] found that the rs2910164 CC genotype is associated with significantly increased susceptibility to GC (OR = 1.30; 95%CI: 1.02-1.66, $P = 0.03$) and Song *et al*[153] reported that miR-146a rs2910164 CC carriers had a significantly increased risk of IM (OR = 1.42, 95%CI: 1.03-1.97) and dysplasia (OR = 1.54, 95%CI: 1.05-2.25) as compared with GG carriers and when stratified the analysis by *H. pylori* infection status found that rs2910164 C allele was associated with an increased risk of IM and dysplasia only among individuals with *H. pylori* (CC *vs* GG: OR = 1.53, 95%CI: 1.12-2.08, $P < 0.05$), suggesting that mir-146a rs2910164 polymorphism might promote the occurrence of IM and dysplasia jointly with *H. pylori* infection.

However, Zeng *et al*[154] found that subjects with GG and GC genotypes had a 58% increased risk of GC (adjusted OR = 1.58; 95%CI: 1.11-2.20, $P < 0.01$) and another Japanese study revealed the combined effect of miR-146a rs2910164 G/G and TLR4 +3725 C allele on the increased risk of severe gastric atrophy among the *H. pylori*-infected Japanese subjects[155]. Besides, in an European population various gene polymorphisms including miR-146a (G>C rs2910164) were not associated with the presence of high risk atrophic gastritis or GC[156]. Nevertheless, three recently published meta-analysis concluded that miR-146a rs2910164 GG or GC polymorphisms are associated with increased susceptibility to GC, especially in Asian population[157-159].

H. pylori CagA(+) was shown to decrease let-7 expression in the gastric epithelium and let-7 family expression levels have been shown to be negatively

associated with histological scores for activity, chronic inflammation and *H. pylori* density[11,68]. The let-7 family acts as tumor suppressors and its target genes are oncogenes such as Ras, c-myc and HMGA2 (high mobility group A2)[160,161]. Indeed, miR-7 is downregulated in GC and it has been shown that pre-miR-7 transfection into GC cells suppresses cell proliferation and colony formation, while let-7b knockdown was associated with growth promotion, migration and invasion[71,162]. Lower levels of let-7b were also found in *H. pylori* -infected and in GC tissues and collagen triple helix repeat containing 1 was found to be its direct target[162]. Let-7d downregulation was also associated with oncogene overexpression contributing to carcinogenesis.

H. pylori induces an invasive phenotype in epithelial cells that resembles EMT through the disruption of cell-cell junction and loss of apical-basolateral polarity mediated by the interaction of CagA with several junction proteins like ZO-1, JAM and E-cadherin[18,163]. *H. pylori* CagA is also associated with B-catenin release from E-cadherin and subsequent activation of Wnt/B-catenin signaling pathway, and deregulation of B-catenin seems to play a crucial role in GI cancers[164]. *H. pylori* CagA transfect into gastric epithelial cells results in miR-584 and miR-1290 upregulation, *via* NF-κB and Erk1/2 respectively[110]. miR-1290 was also implied in miR-584 activation. Foxa1 and Smad2 were identified as targets of miR-584 and miR-1290 and knockdown of Foxa1 was shown to promote EMT in GC cell lines. Overexpression of miR-584 and/or miR-1290 was also associated with decreased E-cadherin levels, suggesting that Foxa1 downregulation by miR-584 and miR-1290 promotes EMT. Overexpression of miR-584 and miR-1290 was also associated with the development of intestinal metaplasia through interference with cell differentiation and remodeling of gastric mucosa[110].

The miR-200 family (miR-200a,b,c, miR-141, miR-429) was also associated with epithelial differentiation and suppression of EMT in several types of cancers by inhibition of ZEB 1 and 2 (Zinc-finger E-box Binding homeobox 1 and 2 - transcriptional repressors of E-cadherin)[165,166]. In GC low miR-200b expression was associated with tumor size, LNM and lymphatic invasion and a strong correlation was found between miR-200b, ZEB2 and E-cadherin mRNA, *i.e.,* in cells overexpressing miR-200b ZEB2 mRNA levels were lower and E-cadherin expression levels were increased, which was associated with significantly reduced cellular proliferation, and inhibition of cellular migration and invasion, suggesting that miR-200b is a tumor suppressor miRNA[167]. ZEB2 also represses cyclin D1 transcription, a cyclin that promotes G1/S transition and is induced *via* AP-I in gastric epithelial cells during *H. pylori* infection and under CagA dependence[168]. The above findings suggest a role for miR-200 family and ZEB repression in the EMT-like phenotype in *H. pylori*-infected cells. miR-141, decreased in *H. pylori* -infected gastric tissue[11] targets fibroblast growth factor receptor (FGFR), and overexpression of miR-141 leads to decreased FGFR2 expression and inhibition of proliferation[169].

MiR-375 repression and B-catenin-activating mutation also was described in hepatocellular adenoma and carcinoma[170]. Ye *at al*[171] demonstrated that *H. pylori* LPS deregulates miR-375 and miR-106b expression in gastric epithelial cells and that downregulation of miR-375 was associated with increased expression of MDM2 (E3 ubiquitin-protein ligase Mdm2), an important negative regulator of the p53 tumor suppressor. *H. pylori* LPS also enhanced the tyrosine phosphorylation of JAK1, JAK2 and STAT3, and JAK1 and STAT3 were found as target genes of miR-106b, suggesting that *H. pylori* LPS may enhance JAK/STAT3 pathway *via* inhibition of miR-375 and miR-106b. These findings were confirmed in a recent study where it was found that *H. pylori* infection downregulates miR-375, which targets JAK2/STAT3. In these study, gain-of-function and loss-of-function experiments have shown that decreased miR-375 expression mimics the oncogenic effects of the JAK2/STAT3 pathway (which promotes neoplastic transformation by affecting the expression of Bcl-2 and TWIST1) and that treatment with siRNAs targeting JAK2 prevents proliferation and migration even in response to *H. pylori* infection[172]. In accordance with these findings, another study showed miR-375 downregulation in GC and miR-375 was found to reduce cell viability by targeting 14-3-3 zeta, an anti-apoptotic protein that promotes cell survival by binding to Bad, a pro-apoptotic protein[173]. PDK1 (3-phosphoinositide dependent protein kinase), a kinase that directly phosphorylates Akt and thereby regulates the PI3K/Akt signaling pathway was also identified as a direct target of miR-375.

TGF-β is involved in mucosal immunity and in the control of the physiological turnover of epithelial cells, and the downstream effectors of TFGB-dependent cell cycle arrest and apoptosis are the CDK inhibitor $p21^{CIP1/WAF1}$ and the pro-apoptotic factor Bim, respectively. miR-25, miR-93, miR-106b, and miR-130 inhibit apoptosis by preventing the expression of the pro-apoptotic protein, Bim[174]. The miR-106b-25 cluster (miR-106b, miR-93 and miR-25) was demonstrated to be abnormally upregulated in GC and it was associated with decreased response of gastric cells to TGF-β by interfering with the expression of p21 and Bim, affecting both cell cycle and apoptosis[120,175]. Indeed, miR-106b-25 cluster was found to silence $p21^{CIP1/WAF1}$, E2F1 and the proapoptotic factor Bim leading to a decreased response of gastric cells to the TGFb tumor-suppressor activity and to impairment of p21 tumor suppressor activities[120,174]. MiR-25 was also found to target and negatively influence Bim and the CDK inhibitors p27 and p57[176].

miR-130b and miR-301a are both upregulated in GC and may contribute to tumorigenesis and invasion by downregulation of Runx3 expression[177]. Overexpression of miR-130b in GC was demonstrated and it is believed to contribute to suppression of Bim in TGF-β media-

ted apoptosis by targeting RUNX3, a known tumor suppressor silenced by promoter hypermethylation in GC[178,179]. mir-301a was also reported to be upregulated in GC, and directly downregulates Runx3 expression[180]. Together these findings suggest that overexpression of these oncogenic miRNAs results in activation of CDK2 (promoting G1/S phase progression) and in impairment of the TGF-β mediated tumor suppressor pathways that may be critical steps in the development of gastric tumors.

miR-524-5p was also found to suppress cancer cell proliferation and invasion by downregulating Jagged-1 and Hes-1, two key components of the Notch signaling pathway[181] and it was suggested that miR-524-5p may also be involved in GC by regulating cell cycle and TGF-β signaling pathway[118]. miR-449, a tumor suppressor miRNA both downregulated in *H. pylori*-infected gastric mucosa and in GC, targets cyclin E2 and geminin (promoters of G1/S and M/G1 cell cycle progression), suggesting that miR-449 downregulation may be important in cell cycle progression and proliferation[182]. miR-449 was also found to target Met, geminin, and SIRT1, proto-oncogenes that may be related with proliferation, angiogenesis, invasion and metastasis[182].

miR-203 expression was found to be lower in *H. pylori*-positive tissues (both tumoral and non-tumoral) and in GC cell lines and miR-203 was found to directly target CASK (calcium/calmodulin-dependent serine protein kinase, a cytoskeletal protein overexpressed in various cancers)[183]. Indeed, CASK expression was found to be significantly higher in *H. pylori*-positive cells and was inversely correlated with miR-203 levels. Furthermore, miR-203 transfection could inhibit cell growth, colony formation and cell invasion, suggesting its potential tumor suppressor role in *H. pylori*-induced GC[183].

mir-29a is also significantly downregulated in GC and it targets p42.3 which regulates G2/M progression and promotes cell cycle progression and proliferation[184,185]. miR-29c is a tumor-suppressor miRNA significantly downregulated in GC tissues compared with non-tumoral gastric mucosa[186]. Treatment with celecoxib, a selective COX-2 inhibitor, significantly activates miR-29c expression suppressing anti-apoptotic Mcl-1[108,187]. This pathway could be one of the mechanisms of the chemopreventive effects of selective COX-2 inhibitors and suggesting that selective iCOX-2 may be a clinical option for the treatment of GC *via* restoration of mir-29c.

miR-181b is increased early after *H. pylori* infection, returns to normal levels early after *H. pylori* treatment (72h) and is upregulated in GC[188]. Timp3 (tissue inhibitor of MMP-3 and a pro-apoptotic factor), was identified as a direct target of miR-181 and miR-181b overexpression was associated with inhibition of apoptosis, cell proliferation, invasion and migration in GC cells. Timp3 downregulation in esophageal and GC has been linked with epigenetic changes namely gene methylation[189,190]. Together these data suggest that *H. pylori* infection can promote gastric carcinogenesis through miR-181b upregulation which leads to decreasing Timp3 levels, promoting proliferation, migration and invasion.

miR-223 is also overexpressed in GC and was suggested as an useful serum biomarker for its detection. Significantly higher levels of miR-223 were found in *H. pylori* -infected GC patients and in healthy controls with *H. pylori* infection (*vs* those without)[191]. In another study, Li *et al*[192] found that miR-223 was associated with migration and invasion through downregulation of erythrocyte membrane protein band 4.1-like3 (EPB-41L3). Besides, miR-223 upregulation was associated with higher proliferation, colony formation, migration and invasion of *H. pylori*-positive GC cells[193]. mir-27a has been identified as an oncogenic miRNA in GC by targeting the tumor suppressor prohibitin and FOXO1 (forkhead box protein O1), which may protect cells against oxidative stress[194-196].

Bcl-2 superfamily are a group of anti-apoptotic proteins whose expression can be regulated by tumor suppressor miRNAs (*e.g.,* miR-15b, miR-16, miR-34, miR-181b, miR-181c, and miR-497). These miRNA clusters are downregulated in GC cells leading to increased expression of Bcl-2 and inhibition of apoptosis[197]. In *H. pylori*-infected gastric mucosa miR-200bc/429 cluster is downregulated increasing expression of Bcl-2 and XIAP and thus inhibiting apoptosis[194,195,198].

Another tumor suppressor miRNA, mir-218 is significantly decreased in both *H. pylori*-infected mucosa and in GC tissues[199]. MiR-218 was shown to induce apoptosis in GC cells through direct targeting of epidermal growth factor receptor-co-amplified and overexpressed protein (ECOP) leading to inhibition of NF-κB transcriptional activation and inhibition of COX-2 transcription, leading to an apoptotic response[199]. miR-218 downregulation in GC cells was also correlated with increased metastasis and invasion through SLIT/ROBO1 signaling pathway upregulation[65,199,200]. Thus it seems that downregulation of miR-218 in GC cause ECOP overexpression, activation of NF-κB activity and COX-2 transcription, ultimately inhibiting apoptosis and inducing cell proliferation[199]. Tables 2 and 3 summarize the microRNAs that have been found to have a role in *H. pylori* -related gastric carcinogenesis. MicroRNAs overexpressed in GC generally target and repress tumor suppressor genes functioning as oncogenic miRNAs (Table 2), while tumor suppressor miRNAs that target and repress oncogenes are downregulated in GC (Table 3).

EFFECTS OF *H. PYLORI* ERADICATION ON MICRORNAS

The effect of *H. pylori* eradication on reducing GC incidence is believed to be related to the risk existing at the time of eradication therapy[201]. A systematic review suggested that atrophic gastritis can undergo regression within one or two years after successful eradication of *H.*

Table 2 Potential oncogenic microRNAs

MicroRNA	*H. pylori*	GC	Targets	Consequences/associations
miR-21	↑	↑	RECK	Decreased apoptosis; cell proliferation, invasion
			PTEN	MMP stimulation
			ABP	PI3K/Akt signaling pathway activation
miR-106a			RB1	E2F transcription; lymphatic and distant metastasis
miR-584	↑		Foxa1	EMT promotion; decreased E-cadherin
miR-1290			SMAD2	Cell differentiation and remodeling; IM development
miR-296-5p		↑	CDX1	Erk1/2 activation; growth promotion
miR-222	↑	↑	RECK	Proliferation
miR-223	↑	↑	EPB41L3	Migration and invasion
miR-106b-25 cluster		↑	$p21^{CIP1/WAF1}$	Decreased response to TGF-B
			Bim	Cell cycle progression; inhibition of apoptosis
			E2F1	
miR-130b		↑	RUNX3 | Bim	Proliferation (CDK2 activation) and invasion
miR-301a			RUNX3	Apoptosis inhibition
miR-181b	↑	↑	Timp3	Inhibition of apoptosis, cell proliferation, invasion and migration
miR-27a	↑	↑	FoxO1	Increased oxidative stress
			Prohibitin	

H. pylori: *Helicobacter pylori*; GC: Gastric cancer; RECK: Reversion-inducing cysteine-rich protein with Kazal motifs; PTEN: Phosphatase and tensin homolog; ABP: Androgen-binding protein; MMP: Matrix metalloproteinase; PI3K: Phosphoinositide 3-kinase; E2F: E2F family; Foxa1: Forkhead box protein A1; SMAD2: Mothers against decapentaplegic homolog 2; EMT: Epithelial-mesenchymal transition; IM: Intestinal metaplasia; CDX1: Caudal type homeobox 1; Erk: Extracellular-signal-regulated kinases; EPB41L3: Erythrocyte membrane protein band 4.1-like 3; p21: Cyclin-dependent kinase inhibitor 1; Bim: Bim gene (Bcl-2 family member); TGF-B: Transforming growth factor beta; RUNX3: Runt-related transcription factor 3; Timp3: TIMP Metallopeptidase Inhibitor 3; FoxO1: Forkhead box protein O1.

pylori[202].

However regression of atrophic gastritis after *H. pylori* eradication seems to depend on the size and topographical distribution of atrophy, with a subsequent meta-analysis suggesting that gastric atrophic changes could only be reversible in cases located in the corpus but not in the antrum[203]. The presence of IM is a less reversible stage than atrophy alone, with meta-analysis suggesting that eradication at the IM stage is less effective and more likely to progress[203]. Lower *H. pylori* colonization of areas with IM may explain why the advantage of eradication is more limited at this stage. However, even if *H. pylori* eradication can't regress intestinal metaplasia, it may be beneficial in decreasing cancer risk in patients with widespread IM, as suggested in a Japanese multicenter study which showed that incidence of new cancers was reduced by one-third among those with *H. pylori* eradication compared with those without eradication therapy[204]. Despite this, GC still arises in the setting of IM even following *H. pylori* eradication and evidence concerning the ability of *H. pylori* eradication to reduce the risk of cancer in cases of widespread IM is lacking, though it seems to reduce progression.

Several studies recently assessed the potential benefits of *H. pylori* eradication on the miRNA deregulation and methylation status of the gastric mucosa. Indeed, aberrant methylation and methylation levels of CDH1 are reported to decrease after *H. pylori* eradication, suggesting that DNA methylation in gastric mucosa decreases when *H. pylori* is eradicated[101]. However, Ando *et al*[96] found that methylation levels of miR-124 were not decreased in individuals with past infection when compared to patients with current infection, suggesting that aberrant methylation induced in set cells may persist even after *H. pylori* eradication.

Shiotani *et al*[117] evaluated the expression of 21 miRNAs in gastric biopsies before and after *H. pylori* eradication in patients with history of endoscopically resected early GC and non-cancer controls and found that the expression of oncogenic miRNAs was significantly higher in the intestinal metaplastic glands than in the non-intestinal metaplastic glands, irrespective of *H. pylori* eradication. In neither group *H. pylori* eradication significantly changed any miRNA expression in the intestinal metaplastic glands, despite a beneficial effect of *H. pylori* eradication was seen in the control group where eradication decreased miR-223 expression and let-7d expression increased. The authors then concluded that *H. pylori* eradication improved miRNA deregulation but not in intestinal metaplastic glands[117], further supporting the clinical finding that intestinal metaplasia is a less reversible stage in the gastric carcinogenesis.

In another study by Shiotani *et al*[205], expression of serum miRNAs was evaluated in patients with history of endoscopically resected EGC and age and sex matched controls, before and one year after *H. pylori* eradication and it was found *H. pylori* eradication significantly decreased miR-106b levels and increased let-7d only in the control group.

Altogether these findings suggest that despite *H. pylori* eradication seems to be of benefit in the improvement of miRNA deregulation, some underlying processes may continue to promote tissue damage and contribute to the progression of the gastric carcinogenesis.

Table 3 Potential tumor suppressor microRNAs

MicroRNA	*H. pylori*	GC	Targets	Consequences/associations
miR-185	↓		DNMT1 and EZH2	DNA methylation; proliferation; EMT; LNM; poor prognosis
miR-204	↓		SIRT1	EMT; invasion
miR-106b	↓			Proliferation (TGF-B induced cell cycle arrest suppression)
miR-320	↓	↓	Mcl-1	Apoptosis inhibition; progression of prenoplastic conditions Relapse of tumors; chemoterapeutic resistance
miR-101, miR-515-5p	↓	↓	Mcl-1 SOC2; DNMT1	Apoptosis inhibition Let-7 attenuation
miR-490-3p	↓	↓	Cyclin B1 SMARCD1	EMT; proliferation; colony formation; migration; invasion Metastasis and poorer survival Decreased through the spectrum of gastric carcinogenesis
miR-370	↓	↓	FoxM1	↓p27 expression; cell cycle progression and proliferation Decreased through the spectrum of gastric carcinogenesis
miR-328	↓		CD44v9	Survival and proliferation of metaplastic cells
Let-7	↓	↓	Ras c-myc HMGA2 Cthrc1	Cell proliferation and colony formation Migration and invasion
miR-200, miR-141, miR-429	↓	↓	ZEB1/2 Cyclin D1 Bcl-2|XIAP	Epithelial differentiation; EMT suppression Decreased E-cadherin, inhibition of migration and invasion Proliferation Apoptosis inhibition Tumor size, lymphatic invasion and LNM
miR-141	↓		FGFR2	Proliferation
miR-375	↓	↓	MDM2 JAK2/STAT3 3/3/2014 PDK1	p53 inactivation Neoplastic transformation; proliferation and migration Inhibition of apoptosis PI3K/Akt signaling pathway activation
miR-524-5p		↓	Jagged-1; Hes-1	Cell proliferation and invasion
miR-449	↓	↓	Cyclin E2|Met Gemini|SIRT1	Proliferation, angiogenesis, invasion and metastasis
miR-203	↓	↓	CASK	Cell growth, colony formation and cell invasion
miR-29a miR-29c		↓	p42.3; Mcl-1	Cell cycle progression and proliferation
miR-15b, 16, 34, 181b, 497		↓	Bcl-2	Apoptosis inhibition
miR-218	↓	↓	ECOP SLIT/ROBO1	Activation of NF-κB and increased COX-2; apoptosis inhibition Invasion and metastasis

H. pylori: *Helicobacter pylori*; GC: Gastric cancer; DNMT1: DNA (cytosine-5)-methyltransferase 1; EZH2: Enhancer of zeste homolog 2; EMT: Epithelial-mesenchymal transition; LNM: Lymph node metastasis; SIRT1: Sirtuin 1; TGF-B: Transforming growth factor beta; Mcl1: Myeloid cell leukemia 1; SOC2: Suppressor of clear homolog; SMARCD1: SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily D member 1; FoxM1: Forkhead box protein M1; HMGA2: High-mobility group AT-hook 2; Cthrc1: Collagen triple helix repeat containing 1; ZEB1/2: Zinc finger E-box binding homeobox 1/2; XIAP: X-linked inhibitor of apoptosis protein; FGFR2: Fibroblast growth factor receptor 2; MDM2: Mouse double minute 2 homolog; JAK1: Janus kinase 1; STAT3: Signal transducer and activator of transcription 3; PDK1: Phosphoinositide-dependent kinase-1; Hes-1: Hairy and enhancer of split-1; CASK: Calcium/calmodulin-dependent serine protein kinase; ECOP: EGFR-coamplified and overexpressed protein; NF-κB: Nuclear factor kappa B; COX-2: Cyclooxygenase-2.

CONCLUSION

H. pylori infection is a key factor in gastric carcinogenesis and influences inflammation, proliferation, cell cycle progression and apoptosis, differentiation, migration and invasion. Chronic *H. pylori* gastritis results from both innate and adaptive immune responses that seem to be tightly regulated by miRNA. The inflammatory milieu within the gastric mucosa contributes do DNA methylation of tumor suppressor genes and to the accumulation of both genetic and epigenetic alterations in gastric epithelial cells, contributing to the progression of gastric carcinogenesis. Several studies implicate miRNA in DNA methylation and in the regulation of several inflammatory and neoplastic pathways including in GC. However, each miRNA can control the expression of hundreds to thousands of genes, making difficult to unravel all the processes under miRNA control and thus we are just beginning to understand the genetic and molecular mechanisms underlying the process of gastric carcinogenesis. Nevertheless, the existing studies allow us to understand the importance of these small non-coding nucleotides and to link inflammatory pathways to neoplastic transformation at a genetic level, despite some studies come from animal models and some inconsistencies exist in the literature concerning the function of some miRNAs.

Further studies are undoubtedly needed to continue to improve our knowledge about miRNA functions in *H. pylori* -related GC, both at a genetic and at a clinical level in order to bring miRNAs to clinical practice as markers of disease and as prognostic markers and one day epigenetic therapy may have a role in the treatment of patients with preneoplastic conditions after *H.*

pylori eradication and GC *via* downregulation of onco-miRNAs and activation of tumor suppressor miRNAs. Given the data summarized in this review, we believe that let-7, miR-106 family, miR-146a, miR-155, miR-181b, miR-223 and miR-375 are the miRNAs most consistently reported to have important roles in gastric *H. pylori*-related carcinogenesis and thus we suggest that these miRNAs deserve greater attention in clinical studies to found if they can be used as disease markers. Future studies on this topic should focus on both miRNA serum and tissue levels in patients in different stages of gastric carcinogenesis (not infected with *H. pylori*, chronic *H. pylori* gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, invasive carcinoma and metastatic carcinoma). Furthermore, we believe that the modulation of miRNAs by *H. pylori* eradication and chemoprevention with COX-2 should also deserve attention in future studies.

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