Review Article

Epigenetic alterations in *Helicobacter pylori* infection leading to gastric carcinogenesis: A systematic review

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Background: Gastric cancer (GC) is one of the top causes of cancer death worldwide, with 98% caused by *Helicobacter pylori*. The diverse disease presentation, asymptomatic *H. pylori* infection, and ineffective therapies lead to late diagnosis and high mortality. Chronic inflammation caused by *H. pylori* causes genetic and epigenetic modifications. Hence, this systematic review will address *H. pylori*-related DNA methylation, histone modifications, and RNA alteration in GC. **Materials and Methods:** A comprehensive search of PubMed and Scopus was performed for publications from 2017 to August 2022. Studies involving GC regardless of type and location, *H. pylori* infection regardless of virulence factors, and epigenetic changes (DNA methylation, histone modification, and RNA alteration) were included. Studies of epigenetic changes in GC unrelated to *H. pylori* were excluded. All types of studies were taken into the analysis. **Results:** A final analysis includes 26 manuscripts, comprising 10 reviews and 16 original articles. Methylation levels in various gene promoters having a role in host defense, cell integrity and cell cycle, DNA repair, and apoptosis were altered in *H. pylori* infection preceding GC. In addition, *H. pylori* regulate specific genes through histone modifications. Different MicroRNA expressions were found in H. pylori GC patients, some acting as a tumor suppressor and influencing drug resistance. H. pylori eradication, to a certain extent of disease, can revert these epigenetic changes. **Conclusion:** Understanding the exact mechanism leading to carcinogenesis is required for GC early diagnosis and precise therapy to alleviate the disease burden.

Key words: *Helicobacter pylori*, histone, infectious disease, microRNAs, virulence

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INTRODUCTION

Helicobacter pylori, a bacterium inhabiting the stomach, is highly related to carcinogenesis development.[1] It is found to increase gastric cancer (GC) odds ratio of 5.9 times in 10 years within infection.[2] In 2020, GC was in the fourth place for cancer deaths worldwide, with 1 million new cases. The high mortality was contributed

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by diverse disease presentations, leading to late diagnosis and insufficient effective therapies.[3] Most of this disease occurred in East Asia and the male population.[4] Even though multiple molecular biomarkers for GC have been found, the study of the molecular process involving the primary cause of GC is scarce.

With only 1%–3% of people colonized by *H. pylori* developing cancer,[5] *H. pylori* causes approximately 98% of all GC cases.[6] Various combinations of three to four antibiotics have been proposed as *H. pylori* eradication therapy, with a high rate of resistance worldwide.[7] The risk factor for the infection includes poor hygiene and low economic level.[8] Cytotoxin-associated gene A (*cagA*) and vacuolating cytotoxin A (*vacA*), two virulence factors owned by the bacteria, can induce genetic mutations.[9] Despite carrying various virulence factors able to disrupt signaling pathways in the human body, chronic inflammation of *H. pylori* triggered posttranslational modification in genes.[10] Both genetic and epigenetic modification of protooncogenes and tumor-suppressor genes result in the development of cancer.[11] Widely known epigenetic changes related to *H. pylori* carcinogenesis are hypermethylation in gene promoters.[12] The collection of abnormal methylation in chronic infection creates an "epigenetic field defect" prone to GC.[13] In addition to DNA methylation, few histone modifications and altered ncRNA expression have been found as probable mechanisms.[6]

As epigenetic modification is a dynamic process, a comprehensive understanding of epigenetic changes could provide an alternative for emerging biomarkers and epigenetic therapy for GC. While *H. pylori* is a significant risk factor, knowing the process related to its infection is imperative. Understanding the specific molecular process to identify susceptible populations will help reduce the disease burden. This systematic review addressed the epigenetic mechanism in *H. pylori*-related GC. Hence, the knowledge could be used as diagnostic and therapeutic initiatives to reduce GC mortality.

MATERIALS AND METHODS

Eligibility criteria

We include studies covering GC of any type and location (both cardia and noncardia) regardless of any demographic characteristics. The inclusion criteria include *H. pylori* infection regardless of *CagA* status and epigenetic changes (DNA methylation, histone modification, and RNA alteration). All studies addressing the relation between GC and the above were included. We excluded studies mentioning epigenetic changes in GC not caused by *H. pylori* and epigenetic therapies.

Information sources

We searched PubMed and Scopus. We include papers from 2017 to 2022. The following terms were searched: gastric cancer OR gastric carcinogenesis OR stomach cancer AND *H. pylori* OR *H. pylori* AND epigenetic OR epigenetic changes OR epigenetic modification. All articles must be in English.

Study selection

The search results from all databases were combined. The author screened the title and abstracts and then excluded unqualified studies. Afterward, the full text was retrieved for further evaluation. The complete flow of the study selection is presented in Figure 1.

RESULTS

We included 26 manuscripts in our study. Most studies were excluded due to not mentioning specific *H. pylori*-related epigenetic changes.

Epigenetic modification in gastric cancer

GC is in the top five cancer[14] worldwide[15] and is the second for cancer-related deaths.[16] It is the final consequence of genetic and epigenetic alterations.[17] As a risk factor for this disease,[18] *H. pylori* has been reported to elicit multiple modifications through its chronic inflammation pathways.[19] Despite being classified by the World Health Organization as a Group I carcinogen,[16] the exact mechanism of how *H. pylori* induce cancer has been investigated over the years. In *H. pylori* infection, methylation levels were generally increased, even in noncancerous mucosa of GC patients.[20] These changes were proposed as the concept of "epigenetic-field-defect" predisposing to carcinogenesis.[21] Chronic inflammation is recognized as an accelerant to the accumulation of abnormal methylation.[14]

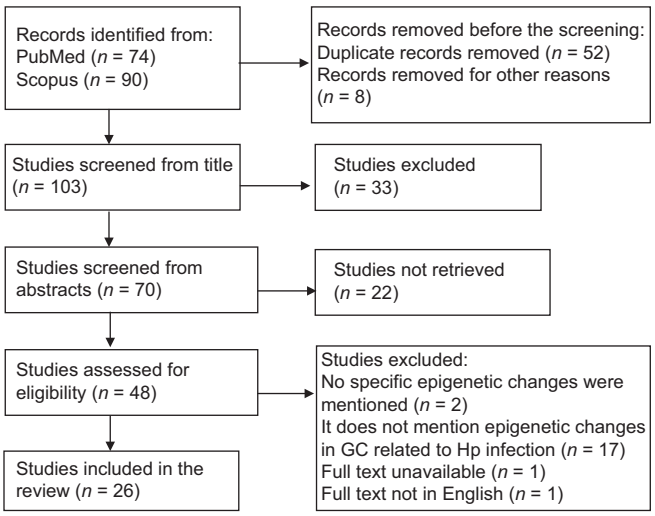

Figure 1: Flow diagram for the study selection based on PRISMA 2020

As DNA methylation is an essential mechanism and can be induced by *H. pylori*, other epigenetic alterations surfaced as possible mechanisms, such as histone modification and MicroRNA (miRNA) alterations. miRNA popularity rises as an essential apparatus for the post-transcriptional regulator, regulating gene expression by disrupting transcription and mRNA cleavage.[22] Studies have proposed miRNA to have a role in GC since it was found to be aberrantly expressed in cancers.[23] Moreover, *H. pylori* infection could upregulate or downregulate particular miRNA, supporting gastric carcinogenesis.[24]

DNA methylation

DNA methylation arises when cytosine in cytosine-guanine dinucleotide is transformed into methylcytosine.[25] The promoter region of genes has these cytosine-guanine-rich regions (CpG islands). In a normal state, most CpG dinucleotides are methylated,[26] except those in CpG islands.[27,28] Through hypermethylation, the binding of transcription factors will be blocked, and the genes lose their expression.[15] Various genes are methylated by *H. pylori* infection, leading to silencing these genes and promoting carcinogenesis.[6,15] DNA methyltransferases (DNMTs) regulate DNA methylation pattern. DNMT expression was higher in *H. pylori*-associated gastritis than in carcinoma, probably due to the lack of inflammation-inducing gastritis in the carcinoma state.[29] A study analyzing methylation patterns in *H. pylori*-related GC found 438 differently methylated regions with 152 regions increased disease risk regardless of the infection status.[30] On the other hand, some studies suggested that *H. pylori* infection's chronic inflammation triggers epigenetic changes instead of the bacteria itself.[31,32] Continuous epigenetic changes in previously normal cells were suggested to predispose them to carcinogenesis.[3]

H. pylori has a unique adaptive mechanism as it can survive and thrive in a hostile gastric environment. Despite neutralizing acidity with urease,[26,33] *H. pylori* bind to gastric mucosa through adhesin and nonadhesin. Human, as the host, has mucins to defend gastric epithelial cells from this pathogen. MUC-17 is a membrane-bound mucin used by the host to limit bacterial adherence and prevent *CagA* translocation and GC cell proliferation through tampering with the NF-B pathway. However, *H. pylori* hypermethylated the MUC-17 promoter, downregulating MUC17 expression.[34] In an array of virulence factors possessed by *H. pylori*,[33] cag pathogenicity island, which encodes the type IV secretion system (T4SS), was related to increased DNA methylation.[15] T4SS can transfer *cagA* and cause morphological changes in gastric epithelial cells called hummingbird phenotypes.[19,26] Consequently, *cagA* causes activation of Raf-MEK-ERK signaling, MAP kinase, activator protein-1 transcription factors, and c-fos and c-jun proto-oncogenes.[26] For the most part, *CagA*-positive *H. pylori* infection had substantial methylation compared to Cag-A negatives.[33]

The inflammation caused by *H. pylori* activates multiple cytokines originating from T-helper 1 (Th-1), Th-2, Th-17, and T-regulatory.[25,26] These cytokines activate Janus kinase 2 (JAK-2), which subsequently phosphorylates signal transducers and activators of transcription 3 (STAT3). STAT 3 will then go into the nucleus to regulate genes. JAK/STAT cascade is negatively modulated by the suppressor of cytokine signaling 1 (*SOCS-1*). *H. pylori* induces methylation in *SOCS-1* promotors, increasing cytokine production and leading to GC.[25] Moreover, the increased cytokine production, such as interleukin-1β (IL-1 β), can induce aberrant DNA methylation.[15,19,33] Chronic *H. pylori* infection increases methylation of the trefoil factor 2 (*TFF2*), rendering wound healing and supporting persistent inflammation.[15,19] Wnt/β-catenin signaling is involved in many cancers as it has a crucial role in cell function.[35] *H.* pylori upregulates Wnt/β-catenin activators by downregulating TFF1 and RUNX3.[6] This pathway is inactivated by promoter methylation of Wnt antagonists such as secreted frizzled-related protein and DICKKOPF (*DKK*), all found upregulated in *H. pylori* infection-related GC.[20] In addition, *H. pylori* infection triggers the expression of caudal-type homeobo × 1 and 2 (*CDX1/2*), which are generally not found in gastric mucosa. *CDX* are transcription factors for the differentiation of the intestinal cell. *CDX1* promoter methylation was low during *H. pylori*-related gastritis and intestinal metaplasia then rose in GC. GC patients with higher *CDX* levels were shown to have a better prognosis. This bimodal action suggests that *CDX* can act as an oncogene and tumor suppressor.[36]

Metastasis in GC is known to be attributed to several gene mutations. However, in the last years, hypermethylation of genes came into light as a contributor to epithelial-mesenchymal transition. Cadherin-1 (*CDH-1*), known as epithelial cadherin (E-cadherin), is pivotal in maintaining cell junction.[37] Loss of *CDH-1* results in the development of metastasis.[38] The gene encoding E-cadherin, *CDH-1*, was genetically and epigenetically altered in cancers.[37-39] CDH-1 hypermethylation level was higher in GC and *H. pylori* infection.[15,19] In addition, *H. pylori* induce hypermethylation of vezatin (*VEZT*),[15] a gene encoding adherents junction transmembrane protein.[40]

Methylation silencing of tumor-suppressor genes by *H. pylori* dismissed the host's natural defense against abnormal changes. Uncontrolled cancer cell growth is contributed by disrupted cell cycle regulation found in the methylation of promoter *CDKN2A*.[15,19] This gene encodes protein acting in the G1 cell cycle.[15] *H. pylori* eradication

reverses the aberrant methylation in *CDKN2A*.[19] Moreover, impairment in autophagy elicits irreparable DNA damage leading to carcinogenesis. *H. pylori* was found to hypermethylate *MAP1LC3A*; the gene for autophagy,[41] *MHL1*; a gene encoding DNA repair protein, and *MGMT*.[15,19] *HUS1* has a role in DNA damage repair and apoptosis, and *INTS1* in DNA damage response was some example of genes hypermethylated by *H. pylori* infection.[12] Macrophages in *H. pylori* infection produce nitric oxides, leading to hypermethylation of *RUNX3* in epithelial cells.[33] With the surmounting methylation of *RUNX3*[15] and forkhead box D3 (*FOXD3*), these gene tumor suppressor function is inactivated.[19,42] *LOX*, which plays an essential role in extracellular matrix assembly,[43] was methylated in *H. pylori* patients.[15] Moreover, *GATA-4* and *GATA-5* were both found to be methylated in GC.[6,19] In *H. pylori*-related GC, downregulated *GATA-5* was seen compared to *H. pylori*-positive gastritis subjects.[44] Both *GATA* is tumor suppressor genes.[6] Reduced *GATA* expression caused cell failure to quit cell cycle.[44] *CYLD* encodes a deubiquitinating enzyme, inhibiting the NF-B pathway, which was deregulated in many cancers. It was suggested to increase resistance to apoptosis when dysregulated.[11,45] Phosphate and tensin homolog (*PTEN*) alterations affect cell cycle, migration, and DNA repair.[46] Both *CYLD*[11] and *PTEN* were reduced in *CagA*-positive *H. pylori* patients.[15,19] Multiple studies have mentioned *H. pylori* eradication to lower DNA methylation. However, methylation level could not regress into the previously noninfected state.[3]

Histone modifications

Histone tails in the chromatin are prone to modification, either acetylation, methylation, phosphorylation, ubiquitylation, or ADP ribosylation.[26] Enhancer of zeste homolog (EZH2) is a significant histone modification apparatus responsible for the trimethylation of a lysine residue in H3. Higher EZH2 expression was found in *H. pylori*-associated gastritis, mucosa adjacent to carcinoma, and GC.[29] Modification in histone H3 serine 10 (H3Ser10) has been reported to involve in carcinogenesis.[47] H3Ser10 has a role in stimulating cancer cells induced by epidermal growth factor, and *H. pylori* infection increases its expression.[19,26] Moreover, H3Ser10 is a mitotic marker in which *H. pylori* affect the cell cycle. The accumulation of phosphorylated H3 was correlated with the poor prognosis in GC patients.[47] In a DNA strand break (DSB) event, after recognition, ataxia-telangiectasia mutated serine/threonine kinase (*ATM*) will induce DSB repairing protein. In *H. pylori* infection, the *ATM* gene can be regulated posttranscriptionally by hyperacetylation of H3/H4.[19,26,48] *ATM* initiation by *H. pylori* requires T4SS and *vacA* secretion.[48] *In* addition, *let-7* expression is reduced by *H. pylori CagA* through histone modification.[49] *H. pylori* infection can induce an epigenetic regulator histone lysine demethylase 4B (KDM4B), which in turn increases IL-8 production and can give rise to tumor migration and invasion.[50]

RNA alterations

miRNA and long noncoding RNA (lncRNA) can regulate gene expressions. miRNA are approximately 20 nucleotides long[38] and can have either oncogenic roles or tumor suppressors. It is expressed differently in diseases, opening the probability for usage as biomarkers.[33] On the other hand, lncRNAs are 200 nucleotides long and originated from the transcription of lagging DNA strands.[51] miR-133, having a suppressor role in multiple cancers,[49] was inhibited through promoter methylation by *H. pylori*.[19] Multiple molecules such as transcription factor Sp1, antiapoptotic molecules, and Bcl-xl are targets of miR-133a. *H. pylori* eradication can undo methylation silencing of miR-133a.[49] miR-204 was downregulated by hypermethylation in *H. pylori*-infected cells and GC.[1] This miRNA repressed the activation of the NF-B pathway. Moreover, it can inhibit the proliferation and metastasis of GC cells *in vivo*.[1] HOXA10, SOX4, and IL-11 are the targets for miR-204.[52] Upregulation of miR-204 could suppress EMT by targeting snai1,[53] and its expression was relieved after *H. pylori* eradication.[33] A study examining miR-193a, a miRNA involved in JAK/STAT signaling, showed that miR-193a is silenced *in vitro*, causing proliferation and metastasis. Clinically, the methylation level was higher in *H. pylori* infection patients.[23] In addition, miR-148a, which inhibits MMP-7 for invasion and migration by E-cadherin cleavage, was downregulated by *H. pylori* infection.[52] miR-370, which regulates cell proliferation, was hindered by *H. pylori*,[51] making way for GC proliferation and migration.[54] *JARID1B*, one of the histone demethylases involved in carcinogenesis, was regulated by miR-29c. In *H. pylori* infection, miR-29c was downregulated, promoting GC cell proliferation through this mechanism.[55] Promoter methylation of miR-133a by *H. pylori* was associated with GC as it targets the Sp1 transcription factor, IGF-1 receptor, and Bcl.[19]

Some miRNA was found to be upregulated in GC. miR-21 took part in the PI3K/AKT signaling pathway to regulate the balance of cell proliferation and apoptosis and was upregulated. Inflammation caused by *H. pylori* leads to the activation of the NF-B signaling pathway, consequently increasing the expression of miR-135b.[52] *H.* pylori-related GC tissue showed an increase in miR-223-3p level,[51] which induces GC proliferation and invasion.[56] Both miR-135b and miR-223-3p inhibit apoptosis and contribute to cisplatin resistance.[52,56] In addition, overexpressed miR-155 by *H. pylori* infection led to GC,[33,51] as miR-155 encouraged cell growth and migration through TGFβR2.[57] miR-155 is abundant in activated B-cells, T-cells, monocytes, and macrophages in chronic gastric inflammation.[24] miR-155 and mir-223 are proportionally increased to Correa's

Table 1: Epigenetic changes in gastric cancer related to *Helicobacter pylori* infection

Epigenetic changes	Study	Epigenetic target	Mechanism	Role in carcinogenesis
DNA methylation	Lin *et al*., 2019[34]	MUC17	Hp downregulate MUC17 expression through hypermethylation of MUC17 promoter regulated by DNMT1	Prevent the translocation of *CagA*
	Muhammad, Eladl and Khoder, 2019; Yousefi *et al*., 2019[15,19]	CDKN2A	Methylation leads to disruption of cell cycle inhibition	Disrupted tumor inhibition
	Muhammad, Eladl and Khoder, 2019; Yousefi *et al*., 2019; Hudler, 2017; George *et al*., 2020[6,15,19,38]	E-cadherin (CDH1 gene)	Methylation induces gene silencing	Onco-suppressor, associated with epithelial-mesenchymal transition
	Muhammad, Eladl and Khoder, 2019; Yousefi *et al*., 2019[15,19]	VZT	Expression is suppressed by hypermethylation of gene promoter	Tumor suppressor
	Yousefi *et al*., 2019[19]	hMHL-1 gene	Hypermethylation in promoter	DNA repair protein
	Muhammad, Eladl and Khoder, 2019[15]	MGMT	Reduced methylation found after Hp eradication	DNA repair protein
	Muhammad, Eladl and Khoder, 2019; Yousefi *et al*., 2019[15,19]	TFF2 gene	Methylation in promoter	Interferes ulcer healing
	Yousefi *et al*., 2019, Vahidi *et al*., 2022[19,33]	RUNX3	Hp accentuate RUNX3 gene promoter methylation	Disrupted tumor inhibition function and several tumor genes
	Muhammad, Eladl and Khoder, 2019[15]	FOXD3	Hp elevate the FOXD3 methylation	Inhibit proliferation, facilitate apoptosis
	Wang *et al*., 2021[12]	HUS1 gene	Hp infection downregulates HUS1 expression through hypermethylation	DNA damage repair and apoptosis
	Wang *et al*., 2021[12]	INTS1	Hp downregulate expression via promoter methylation	DNA damage repair
	Muhammad, Eladl and Khoder, 2019[15]	LOX gene	Highly methylated LOX gene in Hp infection patients	Extracellular matrix remodeling and angiogenesis
	Ghadami *et al*., 2018, Muhammad, Eladl and Khoder, 2019[11,15]	CYLD gene	Hypermethylation reduces CYLD expression	Tumor suppressor
	Muhammad, Eladl and Khoder, 2019[15]	PTEN	Expression level decreased in GC tissues with *CagA* + Hp infection	Apoptosis, cell cycle and proliferation
	Jan *et al*., 2021[25]	SOCS-1	Hp induce SOCS-1 gene promotor, activating JAK/STAT pathway	Increase cytokine production, hyperactivate JAK/STAT pathway
	Alvarez *et al*., 2018[44]	GATA5	Hp induces promoter methylation	Transcription factor
	Yang *et al*., 2017[20]	Wnt antagonist (SFRP and DKK)	Hp methylate SFRP and DKK promoter	Activation of Wnt/-catenin pathway
	Chen *et al*., 2020[36]	CDX	Promoter methylation	Oncogene in IM, tumor suppressor in GC
Histone modification	Yousefi *et al*., 2019; Yang, *et al*., 2018[19,47]	p-H3Ser10	Hp enlarged p-H3Ser10 expression	p-H3Ser10 stimulate neoplastic cells
	Santos *et al*., 2018, Yousefi *et al*., 2019, KZK *et al*., 2020[19,26,48]	ATM gene	Regulate ATM gene via hyperacetylation H3/H4	DSB repair
	Wu *et al*., 2019[50]	KDM4B	Hp induce KDM4B	Increase IL-8 production
RNA-based modification	Pereira *et al*., 2019[52]	miR-21	miR-21 is overexpressed in Hp infection	Alter PI3k/Akt signaling pathway, disturb apoptosis
	Yousefi *et al*., 2019, Gong *et al*., 2022[17,51] Lim *et al*., 2018[49]	miR-133 miR-133a	Hp associated with miR-133 promoter methylation	Ts-miRNA
	Pereira *et al*., 2019[52]	miR-135b	Hp infection induces expression of miR-135b	Inhibit apoptosis, increase cisplatin resistance
	Pereira *et al*., 2019[52]	miR-148a	Hp infection induces downregulation of miR-148a	Inhibition of MMP, induce migration and invasion of GC
	Chen *et al*., 2020; Pereira *et al*., 2019[36,52]	miR-204	miRNA-204 expression is suppressed after Hp infection caused by aberrant promoter methylation	Suppressed TNF, inhibit tumor growth and metastasis
	Gong *et al*., 2022[51]	miR-223-3p	Hp infection increase miR-223-3p level	GC proliferation and invasion, cisplatin resistance

Contd...

Table 1: Contd...

Epigenetic changes	Study	Epigenetic target	Mechanism	Role in carcinogenesis
	Gong *et al*., 2022; Vahidi *et al*., 2022; Link *et al*., 2018[33,51,58]	miR-155	Hp induce overexpression	Cell growth and migration
	Gong *et al*., 2022[51]	miR-370	Hp induce downregulation	Cell proliferation
	Zheng, *et al*., 2021[55]	miR-29c	Hp downregulates miR-29c expression; hence, upregulates JARID1B expression	JARID1B promotes GC cell proliferation
	Wei *et al*., 2021[23]	miR-193a	Methylation of miR-193a is higher in Hp infected patient	Tumor metastasis
	Choi *et al*., 2020[13]	miR-200a/b	Promotor is highly methylated in GC	Tumor suppressor
	Lim *et al*., 2018[49]	Let-7	*CagA* downregulates let-7 expression	Tumor development and progression

Hp=*Helicobacter pylori*; *H. pylori*=*Helicobacter pylori*; GC=Gastric cáncer; VZT=Vezatin; CDH1=Cadherin 1; FOXD3=Forkhead box D3; TFF2=Trefoil factor 2; *CagA*=Cytotoxin-associated gene A; MicroRNA; LOX=Lysyl oxidase; PTEN=Phosphate and tensin homolog; SOCS-1=Suppressor of cytokine signaling 1; SFRP=Secreted frizzled-related protein; DKK=DICKKOPF; CDX=Caudal-type homeobox; ATM=Ataxia-telangiectasia mutated serine/threonine kinase; KDM4B=Demethylase 4B; JAK=Janus kinase; STAT=Signal transducers and activators of transcription; IL=Interleukin; DNMT=DNA methyltransferase; miRNA=MicroRNA; TNF=Tumor necrosis factor; MMP=Matrix metalloproteinase; IM=Intestinal metaplasia

cascade in gastric epithelial cells.[58] miR-200a/b, acting as a tumor suppressor in GC, is highly methylated in GC, reducing its expression. Eradication of *H. pylori* ensued in a decrease in methylation level.[13] Overall, *H. pylori* infection can create pathways deregulation leading to carcinogenesis.

Challenges

GC pathogenesis is inseparable from epigenetic modifications. As *H. pylori* cause most GC, understanding the mechanism of how this bacterium leads to carcinogenesis is essential. *H. pylori* interacts with epithelial cells through various virulence factors, which alter signaling pathways.[59] Hypermethylation of promoters has long been known as an underlying cause besides histone modification and the involvement of miRNA. Chronic inflammation by *H. pylori* enhances the methylation of gene promoters related to the host's protection (e.g., MUC17 and TFF-2), host immune system (e.g., RUNX3 and SOCS-1), epithelial cell integrity (e.g., CDH-1, VZT, and LOX), cell proliferation (e.g., CDKN2A, PTEN, GATA5, and CDX), DNA repair apparatus (e.g., MHL-1, MGMT, HUS1, and INTS1), and apoptosis (e.g., FOXD3, HUS1, and CYLD). Histone modifications of phosphorylated H3Ser10 found in many cancers were also found in *H. pylori*-related GC. In addition, *ATM* and KDM4B genes were regulated through histone modification. Different miRNA expression is identified in *H. pylori*-related GC patients, with some acting as oncogenes, tumor suppressors, or both. Compilations of epigenetic changes in *H. pylori* infection-related GC are compiled in Table 1. Some studies showed that eradicating *H. pylori* reverses the degree of epigenetic changes. However, some showed that these changes are permanent when reaching intestinal metaplasia.

Despite many molecular mechanisms, there were few original articles to be found. The limited sources found probably showed the need for more searching and proving specific genes or miRNAs responsible for the exact process of carcinogenesis. Understanding genomic and epigenomic abnormalities over time is one of the enormous challenges of GC progression stemming from *H. pylori* infection. More in-depth studies are needed to improve GC treatment options. Moreover, identifying the process responsible could be a novel target for GC therapy. Understanding this process would also help to develop drugs with enhanced precision. Overall, finding the genetic and epigenetic alterations in *H. pylori* infection preceding cancer is a valuable tool for possible disease detection, improved patient prognosis, and appropriate treatment.

CONCLUSION

Research in genetic and epigenetic alterations in cancer has been developing over the years. However, as the leading cause of GC, the molecular mechanism behind *H. pylori* infection-causing carcinogenesis remained vague. Studies were mostly taken as a one-point event instead of the long-term observations. More studies are needed to broaden our understanding of the *H. pylori* inflammation process to elicit cancer. In addition, having a biomarker specific to GC prognosis and a particular gene or process to target in therapy will vastly improve the morbidity and mortality of GC worldwide.

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Conflicts of interest

There are no conflicts of interest.

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