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REVIEW ARTICLE

Epigenetic Alterations in Gastric Cancer: Mechanisms, Classifications, and Therapeutic Implications

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ABSTRACT: The field of cancer epigenetics has shown that changes beyond genetic mutations play a critical role in tumor development. In gastric cancer, epigenetic alterations significantly affect gene expression, tumor behavior, and clinical outcomes. Modifications such as DNA methylation, histone changes, and non-coding RNAs are now seen as central to disease progression. Environmental factors like *Helicobacter pylori* infection can trigger these changes, leading to abnormal gene regulation and tumor growth. This study explores how epigenetic alterations contribute to the initiation and progression of gastric cancer. Recent research using genome-wide methylation mapping and RNA sequencing has identified key epigenetic changes in gastric tissues. These studies examine the relationship between *H. pylori* infection and DNA methylation, track long-term changes before and after eradication, and analyze how molecular profiles correspond to cancer stages. Many also proposed biomarkers for early detection and targets for therapy. Additionally, epigenetic changes, such as CpG island methylator phenotype and microRNA silencing, appear early and persist throughout progression. While some may be reversible with early intervention, later-stage changes are often permanent. These insights support improved treatment through epigenetic classification, earlier detection, and more personalized therapeutic approaches based on biomarker-driven strategies.

KEYWORDS: Biomedical and Health Sciences, Genetics and Molecular Biology of Disease, Epigenetics, Gastric Cancer, *Helicobacter pylori*, DNA Methylation Biomarkers.

Introduction

Gastric cancer is one of the most aggressive malignancies worldwide; with over one million cases diagnosed and 769,000 deaths every year, it is the fifth most common cancer diagnosed and the third most common cause of cancer death.[1,2] Although treatments like surgery, chemotherapy, and immunotherapy have improved, the survival rate for gastric cancer is low due to late diagnosis and high recurrence rates.

Gastric cancer is a complex disease influenced by genetic, environmental, and infectious factors. Among its most significant risk factors is *Helicobacter pylori*, a Gram-negative bacterium classified by the World Health Organization as a Group I carcinogen. *H. pylori* infections induce chronic gastritis, epithelial injury, and eventually precancerous changes.[3] Epigenetic alterations, such as DNA methylation, histone modifications, and non-coding RNA dysregulation, have been shown to link *H. pylori* infection and other environmental effects to gastric cancer.[4] These modifications influence gene expression without altering the DNA sequence, leading to tumor suppressor silencing, oncogene activation, and cellular pathway disruption. Recent studies have also shown that some epigenetic marks, specifically aberrant DNA methylation, continue even after eradication.[5]

Due to the high mortality rate of gastric cancer and the limitations of current diagnostic techniques, there is an urgent need to identify early, non-invasive biomarkers and develop targeted therapies. Thus, epigenetic modifications present a promising solution: they are detectable in body fluids, reversible under certain conditions, and tightly linked to disease mechanisms.[1] However, there are limitations in translating these findings into everyday medical use. While many epigenetic biomarkers have been identified, few are proven reliable for regular use, and resistance to epigenetic drugs is challenging.[6] This paper reviews recent research to explain how gastric cancer develops, improve how it is classified, and suggest future treatment options. Additionally, this paper argues that epigenetic alterations in gastric cancer, specifically DNA methylation, histone modification, and non-coding RNA problems, play a key role in how the disease starts and grows. These changes can also be categorized in ways that predict outcomes, help with treatment, and serve as targets for new biomarkers and therapies.

Results and Discussion

Foundations of Epigenetic Alterations:

Epigenetic mechanisms, such as DNA methylation, histone modification, and non-coding RNA regulation, play a central role in the development of gastric cancer. These alterations contribute to tumor progression by disrupting gene expression and are often triggered by environmental factors such as *Helicobacter pylori* infection. Due to the aggressiveness of gastric cancer, understanding its underlying mechanisms is key to improving early detection and treatment. While much research has focused on genetic mutations, recent studies have revealed that epigenetic changes also play a vital role in tumorigenesis. These changes can silence tumor suppressor genes, activate oncogenes, and reshape the chromatin without altering the DNA sequence. The primary mechanisms of epigenetic regulation include DNA methylation, histone modifications, and

DOI: 10.36838/IJHSR811.110

non-coding RNAs such as microRNAs and lncRNAs. These are often influenced by environmental and biological factors like *Helicobacter pylori* infection and chronic inflammation that weaken the gastric mucosa. This section investigates how these epigenetic modifications arise and function in gastric cancer.

DNA Methylation:

DNA methylation is one of the most studied epigenetic modifications in gastric cancer because of its link to tumor development. When methylation patterns are disrupted, they can silence important tumor suppressor genes that limit cell growth. A common example is CpG island hypermethylation, which targets the promoter regions of genes like *MLH1* and *CDH1* that are responsible for DNA repair and cell cycle control. When these genes are turned off, it can lead to microsatellite instability (MSI), which happens when the DNA repair system cannot fix mistakes in repeating DNA sections; not only does this increase genomic instability and mutation rate, but it also raises the risk of cancer development.[7,8]

Conversely, global hypomethylation, which occurs when methylation is removed from large regions of the genome, can activate genes that should remain silent. As a result, losing this control can reactivate repetitive DNA, which may lead to chromosome changes and mutations.[9,10] Additionally, oncogenes may become abnormally expressed, leading to even more tumor growth. Together, these effects disrupt normal gene activity, damage genome integrity, and increase mutation rates in gastric tissues.

Several studies also suggest *Helicobacter pylori* infection as a major environmental trigger for epigenetic changes. Chronic inflammation caused by the bacteria stresses the stomach lining and leads to increased activity of DNA methyltransferases (DNMTs), which are the enzymes responsible for adding methyl groups to DNA. Increased DNMT activity can result in abnormal methylation patterns and the silencing of tumor suppressor genes.[5,11] These epigenetic alterations often arise before any visible signs of cancer appear, making DNA methylation both an important early detection signal as well as a potential target for therapy.

Histone Modifications:

Histone proteins serve as structural supports that DNA wraps around, and they can be chemically modified, which influences how tightly the DNA is packaged and whether specific genes are turned on or off. Key types of histone modifications include acetylation (the addition of acetyl groups, usually to loosen the DNA and promote gene expression), methylation (the addition of methyl groups, which can either activate or repress genes depending on the site), phosphorylation (the addition of phosphate groups, often involved in DNA repair and cell cycle regulation), and ubiquitination (the addition of ubiquitin proteins that can signal gene activation or target proteins for degradation). In gastric cancer, abnormal patterns of these modifications can disrupt normal gene expression, promote uncontrolled cell growth, and contribute to resistance against therapies.

A key example is the loss of acetylation on histone proteins H3 and H4. Typically, acetylation makes genes more accessible by loosening the DNA structure. However, when acetylation decreases, the DNA becomes tightly packed, and critical tumor suppressor genes are silenced.[12,13] Thus, this creates conditions in the cell that allow cancer to develop and thrive.

Enzymes called histone deacetylases (HDACs) remove acetyl groups from histones. Many gastric cancer patients have higher levels of HDAC1 and HDAC2, which turn off many genes.[14] Due to their role in silencing tumor suppressor genes, HDACs have become promising targets for cancer drugs. Similarly, enzymes like EZH2, a type of histone methyltransferase, can add methyl groups to specific histones and silence key genes like E-cadherin, which is essential for keeping cells in place.[15,16] When the enzyme is silenced, cancer cells are more likely to undergo epithelial-mesenchymal transition (EMT), a process that allows them to detach, migrate, and invade surrounding tissues. Ultimately, understanding these changes in histone modifications reveals how cancer progresses and introduces new possible therapies to reactivate silenced genes and slow tumor growth.

Histone Modifications:

Non-coding RNAs (ncRNAs), especially microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are becoming key regulators of gene expression in gastric cancer. Although they do not code for proteins, these molecules influence how genes are expressed or silenced. One critical tumor-suppressive miRNA is miR-34a, which regulates cell cycle progression and apoptosis by targeting multiple genes involved in cell survival. In gastric cancer tissues, reducing the expression of miR-34a prevents apoptosis and increases cell proliferation.[17] Another tumor-suppressive miRNA, miR-200c, helps maintain epithelial cell characteristics by targeting EMT-related transcription factors such as ZEB1; when miR-200c levels are low, cells can easily detach and migrate, leading to metastasis.[18] On the other hand, miR-21 acts as an oncogene and is very common in gastric cancer; it promotes cancer cell invasion and spread by repressing the tumor suppressor PTEN. This then activates the PI3K/AKT signaling pathway that supports cell survival and growth.[17]

Additionally, long non-coding RNAs (lncRNAs) play an important role in shaping chromatin structure and epigenetic enzymes, helping to control which genes are turned on or off. For example, LINC00673 has been shown to promote gastric tumor development by leading EZH2 to the promoter regions of tumor suppressor genes; this results in H3K27 trimethylation, a chemical change that silences gene expression and contributes to cancer progression.[19] Another lncRNA, GAS5, has the opposite effect: it is often found at low levels in gastric cancer, helps suppress tumor growth by limiting cell proliferation, and promotes apoptosis through preventing oncogenic signaling pathways.[20] When GAS5 levels drop, growth signals are uncontrolled, which leads to tumor growth and worse patient outcomes.

Furthermore, lncRNAs influence critical pathways such as Wnt/β-catenin and PI3K/AKT. For instance, LINC00152

enhances Wnt/β-catenin signaling and increases the expression of downstream targets like c-MYC and Cyclin D1, which drive cell cycle and tumor progression.[21] These findings show that lncRNAs also contribute to chromatin regulation. Since their expression is often altered in early-stage gastric cancer, non-coding RNAs are promising biomarkers for early detection. Both miRNAs and lncRNAs can shape major pathways and interact with epigenetic enzymes, making them promising treatment options.

Environmental and Biological Triggers:

Environmental and biological factors frequently cause epigenetic changes in gastric cancer. One of the best examples is chronic infection with *Helicobacter pylori* (*H. pylori*) in the stomach lining, which leads to oxidative stress and the release of cytokines. Studies have shown that *H. pylori* infection is directly associated with the hypermethylation of tumor suppressor gene promoters, even in gastric tissues that are not yet cancerous.[5] This indicates that epigenetic changes start to take place in the early stages of disease development, long before any visible tumors are present. **Figure 1** illustrates this epigenetic progression of gastric cancer through stages of inflammation and increasing DNA methylation.

Aside from bacterial infection, the host's immune response plays a key role in epigenetic alterations. During *H. pylori* infection, inflammatory cytokines, such as IL-6 and TNF-α, increase and can heighten the expression of DNMT1, the enzyme responsible for maintaining DNA methylation. As DNMT1 activity rises, methylation of CpG islands occurs throughout the genome and silences genes that are essential for DNA repair and preventing apoptosis.[22] Genetic predisposition also contributes to a person's vulnerability to these epigenetic shifts. Specific single-nucleotide polymorphisms (SNPs) in DNMT1 and other epigenetic regulators have been linked to increased risk of gastric cancer in populations exposed to *H. pylori*. These inherited variants can make some individuals more likely to develop abnormal methylation patterns in response to environmental triggers.[23]

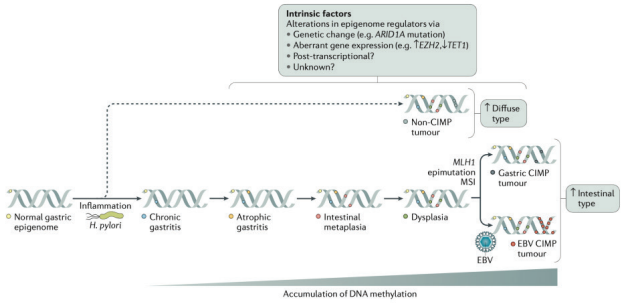

Figure 1: Epigenetic evolution of gastric cancer through inflammation and methylation. This figure shows how the gastric epigenome changes from normal tissue to *H. pylori*-induced inflammation, and then to chronic gastritis, atrophy, intestinal metaplasia, and dysplasia; it also shows a gradual accumulation of DNA methylation. The diagram illustrates how this process can split into non-CIMP tumors (often diffuse type) and CIMP-positive tumors (intestinal type). Adapted from Padmanabhan, N.; Ushijima, T.; Tan, P. How to Stomach an Epigenetic Insult: The Gastric Cancer Epigenome. Nature Reviews Gastroenterology & Hepatology 2017, 14 (8), 467–478. https://doi.org/10.1038/nrgastro.2017.53.

Together, these findings highlight that epigenetic changes in gastric cancer do not occur randomly: they are often affected by chronic infection, signaling, or inherited genetic makeup. Often driven by environmental stressors like *H. pylori*, these alterations alter gene expression without changing the DNA sequence. Thus, their role in silencing tumor suppressors and activating oncogenes makes them promising as biomarkers and therapeutic targets. A visual overview of these regulatory mechanisms is shown in **Figure 2**, highlighting how changes in DNA methylation and non-coding RNA expression contribute to abnormal gene regulation in gastric cancer. Future research should explore how these mechanisms interact and how early intervention might reverse or prevent permanent epigenetic damage.

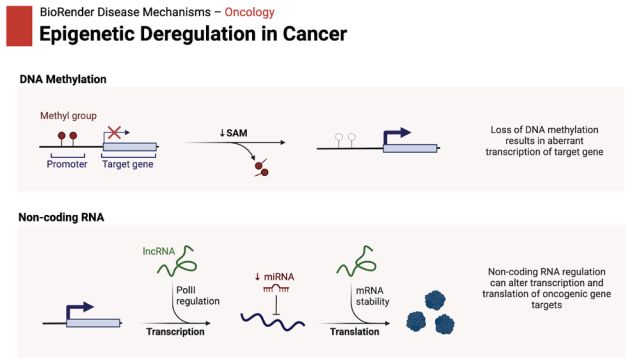

Figure 2: Epigenetic deregulation in cancer. This figure illustrates two key epigenetic mechanisms in cancer: (A) DNA methylation and (B) non-coding RNA regulation. Abnormal DNA methylation, such as promoter hypomethylation or hypermethylation, can lead to dysregulated gene expression. Meanwhile, non-coding RNAs, including lncRNAs and miRNAs, influence transcription and translation as well as impact oncogenic pathways. Created in BioRender. Chiu, J. (2025) https://BioRender.com/k6t23w3

Classifications of Epigenetic Alterations:

Epigenetic changes in gastric cancer can be grouped into specific molecular subtypes that influence how the disease develops and how patients respond to treatment. Unlike random mutations, these changes often follow recognizable patterns linked to certain cancer behaviors. Classification systems like the CpG Island Methylator Phenotype (CIMP) or EBV-related methylation profiles help researchers and doctors organize information, predict outcomes, and create more personalized therapies. Understanding and classifying these epigenetic patterns has become essential for improving diagnosis, prognosis, and precision treatment in gastric cancer.

CpG Island Methylator Phenotype (CIMP):

The CpG Island Methylator Phenotype (CIMP) is when many CpG islands, DNA regions near gene promoters, become abnormally methylated. This often silences tumor suppressor genes that control cell growth, DNA repair, or immune function. Recent studies show that CIMP-high gastric tumors are linked to Epstein–Barr virus (EBV) infection, which causes abnormal methylation across the genome. In EBV-positive tumors, PD-L1 is overexpressed because of epigenetic changes, not gene mutations. This suggests that these patients may respond well to immunotherapy.[24]

DOI: 10.36838/IJHSR811.110

In gastric cancer, hypermethylation of the MLH1 promoter is a key feature of the CIMP-high subtype and is closely associated with microsatellite instability (MSI). This silences the MLH1 gene, weakens DNA repair mechanisms, and allows mutations to build up. By damaging the DNA, these mutations may lead to abnormal proteins or functions that cause uncontrollable growth or cancer. As a result, MSI-high tumors tend to have a high number of neoantigens, making them more responsive to immunotherapy.[25] Furthermore, CIMP-high tumors frequently exhibit methylation of CDKN2A and SOCS1. Methylation of SOCS1 interferes with cytokine signaling regulation, which promotes tumor development due to inflammation. On the other hand, CDKN2A silencing eliminates a crucial stop during the cell cycle, allowing cancer cells to continue multiplying.[26] CIMP-high gastric tumors also have many immune cells around them; they often contain many cytotoxic T cells, possibly due to EBV infection or the high number of mutations caused by MSI.[27]

Environmental and Biological Triggers:

Instead of grouping epigenetic changes only by tumor type or patient outcome, some researchers organize them by their effect on the cell. To do this, they separate gene-silencing from gene-activating methylation. Gene-silencing methylation often shuts down important tumor suppressor genes. For example, when CDH1 is silenced, cancer cells lose their ability to stick together, making them spread more easily.[12] Additionally, the BRCA1 gene repairs DNA, but when it is silenced by methylation, the cell is unable to fix DNA damage properly, possibly leading to more mutations and cancer growth. Conversely, gene-activating changes can happen through hypomethylation, which makes it easier for certain genes to turn on when they should not be. For example, the oncogene c-MYC can become more active when its promoter region is demethylated, leading to uncontrolled cell growth.[28] Researchers also group methylation changes by the types of genes they affect. For instance, methylation of MLH1 is connected to microsatellite instability (MSI) and causes problems with DNA repair. Silencing DAPK1 (a gene involved in programmed cell death) lets cancer cells survive longer than they should, while methylation of CDKN2A removes an important checkpoint in the cell cycle, allowing cancer cells to divide too quickly.[29]

Clinical Utility of Epigenetic Classification:

Classifying gastric cancers by their epigenetic features, such as DNA methylation patterns, can help doctors predict how aggressive the cancer is and which treatments might work best. For example, tumors that are CIMP-high or infected with EBV often have high PD-L1 levels and a strong immune response.[26] Therefore, these patients could benefit from therapies that use the immune system to fight cancer. Another useful subtype is MSI-high, and these tumors often have methylation of the MLH1 gene, which impairs DNA repair. Since MSI-high cancers carry many mutations, they give more neoantigens to the immune system and may respond well to immunotherapy. Finally, knowing a patient's epigenetic subtype can also help determine the best drugs to use. For instance, demethylating agents or HDAC inhibitors may help in cancers with too much methylation or abnormal chromatin regulation. Classifying epigenetic changes in gastric cancer provides important insights into how tumors develop and progress in patients. CIMP, EBV-related methylation patterns, and other gene groupings prove how complex gastric cancer development is. These systems help group patients more accurately, predict outcomes, and guide treatment options. Improving and combining these classifications is the first step to achieving fully personalized therapeutic strategies.

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Therapeutic Implications and Clinical Applications:

As the role of epigenetic alterations in gastric cancer gets clearer, treatments that target them are becoming more common. Drugs that can reverse abnormal DNA methylation and histone changes are being tested in gastric cancer trials. New approaches, like RNA-based therapies, liquid biopsy biomarkers, and combination treatments, also show promise for improving diagnosis and prognosis. These developments underscore the growing potential of epigenetic medicine to transform clinical management and personalize care for gastric cancer patients.

Drugs and Epigenetic Therapies:

Epigenetic therapies are emerging as a new approach in gastric cancer, particularly for tumors marked by DNA methylation or histone modification abnormalities. DNMTs, such as azacitidine and decitabine, can reverse abnormal methylation and reactivate silenced tumor suppressor genes.[30] These treatments are especially useful for early gastric lesions and CIMP-high tumors, which often exhibit widespread promoter hypermethylation.

Histone deacetylase inhibitors (HDACis), such as vorinostat and belinostat, restore normal histone acetylation, which reactivates silenced tumor suppressor genes like PER1 and PER2 and promotes apoptosis in gastric cancer cells.[14] These genes are part of the circadian clock system, which regulates the body's 24-hour biological rhythms (i.e., cell growth, DNA repair, and metabolism). Recent studies using gastric cancer organoids also show that tumors with active RTK/MAPK signaling respond to HDACis, suggesting these drugs may work best in certain molecular subtypes.[31] This supports a more personalized approach to treatment, using pathway activity as a biomarker to guide therapy selection.

New therapeutic targets have also emerged. EZH2, a histone methyltransferase, is common in aggressive gastric cancers and is associated with E-cadherin loss and poor prognosis.[32] EZH2 inhibitors are being studied for their ability to slow tumor growth by changing chromatin structure. In addition, miRNAs and lncRNAs are increasingly recognized for their role in gastric cancer development. RNA-based therapeutics, such as antisense oligonucleotides and small interfering RNAs (siRNAs), target these epigenetic regulators and are being developed to suppress oncogenic RNA species.[33] These therapies are extremely specific, allowing them to directly silence non-coding RNAs that contribute to tumor growth and drug resistance. By adjusting the expression of these RNAs, therapies may reduce harmful traits and reshape cancer cells.

Finally, combining epigenetic treatments with immunotherapy is becoming more popular. For instance, epigenetic modulation can raise PD-L1 levels and attract immune cells, which may improve responses to checkpoint inhibitors in MSI-H and EBV-positive gastric cancers.[34] This effect occurs because epigenetic drugs can turn "cold" tumors (those that avoid detection by the immune system) into "hot" ones that are easier for immune cells to recognize and attack; they do this by exposing hidden tumor antigens, raising MHC levels to help the immune system spot cancer cells, and changing the surrounding areas. Consequently, these combination therapies may offer new treatment options for patients who initially show limited response to immunotherapy.

Biomarkers in Epigenetic Studies:

Epigenetic biomarkers are crucial for identifying gastric cancer patients who may benefit from targeted therapies. With the hypermethylation of genes (i.e., MLH1, CDKN2A, and PCDH10), abnormal DNA methylation remains a key marker and is linked to microsatellite instability and tumor progression.[35] Recently, PRKCB was also identified as a hypermethylated gene that could potentially be used for early detection.[15] The silencing of PRKCB is linked to decreased immune response and poorer outcomes, making it a strong possibility for non-invasive screening and risk assessment in early gastric cancer. Additionally, liquid biopsy technologies that assess circulating tumor DNA (ctDNA) or cell-free DNA (cfDNA) methylation offer a non-invasive approach for diagnosis and recurrence monitoring.[36] These approaches allow clinicians to monitor tumor evolution and treatment response in real time, reducing the need for invasive tissue biopsies and enabling faster clinical decision-making.

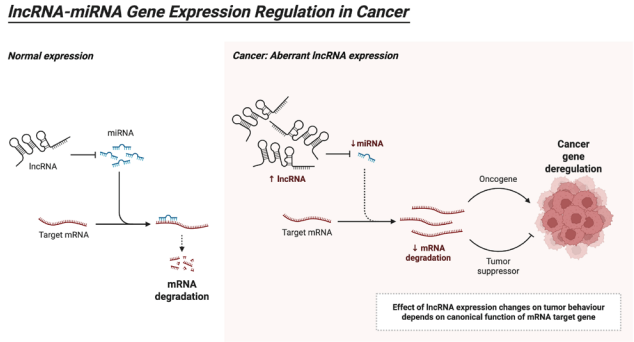

Figure 3: Regulation of gene expression by lncRNA and miRNA in cancer. Dysregulation of the interactions between lncRNA and miRNA alters mRNA degradation as well as contributes to oncogene activation and tumor suppressor silencing in cancer. Under normal conditions (left), lncRNAs regulate miRNA activity, which in turn promotes degradation of target mRNA. In cancer (right), too many lncRNAs or too few miRNAs reduce mRNA breakdown, which causes oncogenes to be overactive or tumor suppressors to be turned off, leading to cancer gene deregulation. Created in BioRender. Chiu, J. (2025) https://BioRender.com/exnv3l1

Aside from DNA methylation, non-coding RNAs and tRNA-derived fragments (tRFs) are recognized as predictive biomarkers. For instance, elevated expression of miR-21 and lncRNA HOTAIR corresponds to poor prognosis and resistance to HDAC and DNMT inhibitors.[37] A model of how altered lncRNA-miRNA interactions impair mRNA degradation and increase cancer gene dysregulation is shown in **Figure 3**. Likewise, measuring plasma tRFs can help detect early gastric cancer and predict outcomes.[38] Together, these biomarkers support precision medicine by improving early detection and treatment response.

Future Directions: Personalized Epigenetic Therapy:

New advances in epigenomics, transcriptomics, and proteomics are transforming gastric cancer treatment by making therapies more personalized. Integrating these multi-omics platforms, technologies that combine data from different biological layers (i.e., DNA, RNA, proteins, and epigenetic changes), helps identify key epigenetic drivers that can guide treatment selection and disease monitoring. Such approaches provide a full picture of the disease, allowing doctors to choose the best treatments based on each tumor's unique profile.[39] This strategy can help overcome barriers like chemoresistance and disease recurrence.

Moreover, a key innovation is the application of patient-derived organoids (PDOs), which retain the genetic and epigenetic characteristics of the patient's tumor. These 3D models are now being used for ex vivo testing of epigenetic therapies, such as DNMT and HDAC inhibitors.[40] In other words, they are practical tools for personalizing treatment and avoiding unnecessary side effects.

Stratification or grouping based on epigenetic risk scores is also proving useful. For instance, aberrant methylation patterns remain in tumors even after treatment, highlighting their potential as long-term markers.[41] After *H. pylori* is removed,

DOI: 10.36838/IJHSR811.110

patients with continued hypermethylation of tumor suppressor genes face a higher risk of the cancer returning.

Additionally, understanding the interaction between epigenetic changes and major oncogenic pathways is essential for advancing targeted therapies. Frequently altered in gastric cancer, this pathway is often influenced by epigenetic modifications, including promoter methylation and histone alterations.[42,43] Modifications can activate or silence genes involved in cell survival, proliferation, and resistance. Targeting both the PI3K/AKT/mTOR pathway and epigenetic regulators may simultaneously help slow tumor growth.

Finally, the role of AI and machine learning in epigenetics is also rapidly expanding. Computational tools using large methylome datasets are being trained to find patterns linked to drug resistance and disease progression.[44] Refining therapeutic decisions and improving patient outcomes, these models can help predict which patients are most likely to benefit from specific epigenetic agents or combination regimens.

Ultimately, these strategies reflect a growing shift toward personalized epigenetic therapy in gastric cancer. Clinicians can now better adjust treatments that work longer, respond better to changes, and are more effective overall. Epigenetic research has revealed powerful insights into the progression and treatment of gastric cancer, leading to the development of promising therapies that target DNA methylation, histone modifications, and non-coding RNAs. The identification of reliable biomarkers is key to optimizing treatment selection, monitoring progression, and guiding personalized care. As technology improves, integrating epigenetic profiles into clinical practice could transform gastric cancer diagnosis.

Conclusion

The concept of epigenetic alterations and their role in the onset and progression of gastric cancer is explained throughout this article, but leaves many unanswered questions. The review began by examining how these epigenetic changes begin, with DNA hypermethylation silencing tumor suppressors, histone-modifying enzymes, and ncRNAs. Environmental triggers, particularly *Helicobacter pylori*, were shown to leave lasting epigenetic damage, even after clearing the infection. Next, the paper discussed how classification systems like CIMP and EBV-related methylation profiles help sort patients by risk and guide treatment. Lastly, the review explored therapeutic and clinical applications, highlighting DNMT and HDAC inhibitors, RNA-based therapeutics, epigenetic–immunotherapy combinations, biomarkers for non- invasive monitoring, and AI-driven models.

Overall, these findings highlight how understanding the epigenetics of gastric cancer can create new precision medicine techniques and more individualized treatment strategies. These insights not only present earlier and more precise detection of the disease using epigenetic biomarkers but also open the door to targeted treatments capable of correcting abnormal patterns of gene silencing or activation.

However, despite recent progress, many questions remain. How can persistent methylation after *H. pylori* eradication be reversed? Can ncRNA-targeting drugs overcome resistance in solid tumors? Which epigenetic changes truly cause cancer, and which are simply linked to it? Future research should combine multi-omics integration and long-term patient monitoring to better track epigenetic changes over time.

Acknowledgments

I would like to thank my mentor, Dr. Shaye, for his invaluable guidance and encouragement throughout the course of this review; his expertise, feedback, and commitment to mentorship played a crucial role in shaping my understanding of the subject and strengthening the quality of this work.

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