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REVIEW

DNA and histone methylation in gastric carcinogenesis

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Abstract

Epigenetic alterations contribute significantly to the development and progression of gastric cancer, one of the leading causes of cancer death worldwide. Epigenetics refers to the number of modifications of the chromatin structure that affect gene expression without altering the primary sequence of DNA, and these changes lead to transcriptional activation or silencing of the gene. Over the years, the study of epigenetic processes has increased, and novel therapeutic approaches that target DNA methylation and histone modifications have emerged. A greater understanding of epigenetics and the therapeutic potential of manipulating these processes is necessary for gastric cancer treatment. Here, we review recent research on the effects of aberrant DNA and histone methylation on the onset and progression of gastric tumors and the development of compounds that target enzymes that regulate the epigenome.

Key words: Epigenetic; DNA methylation; Histone methylation; Gastric cancer; Gastric carcinogenesis

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INTRODUCTION

Gastric cancer (GC) is the fourth most frequent cancer and is the second leading cause of cancer-related death worldwide[1]. Histologically, gastric tumors are divided into intestinal and diffuse types according to the Lauren classification[2]. The intestinal type of GC mostly progresses through the successive steps of normal gastric mucosa, leading to acute and chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and finally a gastric tumor[3]. In contrast, the sequence of events in the development of diffuse type GC is poorly understood, although a subset of diffuse type GC appears to develop independently of atrophic gastritis or intestinal metaplasia[4,5]. Differences in the clinicopathological characteristics between these two histological types indicate that development occurs through distinct molecular pathways[6-10]. Each histological type is a consequence of a progressive accumulation of different genetic and epigenetic alterations.

Epigenetics refers to a number of modifications in the chromatin structure that affect gene expression without altering the primary DNA sequence, and these changes lead to transcriptional activation or silencing of the gene. Interestingly, epigenetic modifications of DNA can also increases mutagenesis and influence the interactions between DNA and carcinogens and ultraviolet light[11]. Epigenetic modifications play a central role in gastric car-

cinogenesis[12]. Recent reports indicate that infection with *Helicobacter pylori* (*H. pylori*) or Epstein-Barr virus (EBV), pathogens with a substantial role in development of GC, are associated with elevated levels of aberrant DNA methylation in GC[13-16]. The study of epigenetic processes has increased in recent years, and novel therapeutic approaches that target DNA methylation and histone modifications have emerged. A greater understanding of epigenetics and the therapeutic potential of intervention into these processes is necessary to help GC treatment.

In this review, after a brief introduction to the methylation machinery, we focus on the roles that aberrant DNA and histone methylation play in the onset and progression of gastric tumors, and the development of compounds that target enzymes that regulate the epigenome.

METHYLATION MACHINERY

DNA methylation refers to the addition or subtraction of a methyl moiety at the 5 position of the cytosine ring within CpG dinucleotides that are usually located in CpG-rich regions or CpG islands and around the gene promoter. DNA methylation in gene promoter regions represses transcription of their downstream genes associated with the suppression of gene expression[17]. However, methylation in gene bodies does not block transcription and is sometimes associated with active transcription[18]. Methylation status is controlled by DNA methyltransferases (DNMT1, DNMT3A, and DNMT3B)[19]. DNMT1 maintains the existing methylation patterns following DNA replication, whereas DNMT3A and DNMT3B target unmethylated CpGs to initiate methylation and are highly expressed during embryogenesis and minimally expressed in adult tissues[20]. Another DNA methyltransferase family member, DNMT3L, interacts with DNMT3A and DNMT3B to facilitate methylation of retrotransposons[21]. Many studies have shown that overexpression of DNA methyltransferases is closely related to tumorigenesis, although the role of DNMT3L in cancer is still unclear (Table 1). In addition, *H. pylori* infection may increase DNA methyltransferase activity through upregulation of the epidermal growth factor and its receptor or via the release of inflammatory mediators, such as nitric oxide[22]. In particular, *DNMT1* overexpression has been associated with EBV infection in GC[23-25].

DNA methylation has also been implicated in the regulation of higher order chromatin structure, the maintenance of genome integrity, and stable patterns of gene expression. These biological effects of DNA methylation are, at least in part, mediated by proteins that preferentially bind to methylated DNA[26]. Methylated DNA is specifically recognized by a set of proteins called methyl-CpG-binding proteins (MBPs), which belong to three different structural families: methyl-CpG binding domain proteins (MBDs), Kaiso domain proteins, and SET and RING finger-associated domain (SRA) domain proteins[27,28]. MBD family proteins (MeCP2, MBD1, MBD2, MBD3 and MBD4) bind methylated CpG (5mCpG) through a conserved protein motif called the methyl-CpG binding domain[29,30]. Over the last decade, proteins that utilize different structures to recognize and bind DNA or its components have been identified. In 2001, Prokhortchouk *et al*[31] identified Kaiso proteins, which bind methylated DNA through a zinc finger motif. Other MBPs including UHRF1 and UHRF2 were identified, and these proteins use the SRA to bind 5mCpG[32,33].

In cancer, the roles of MBPs are related to their functions as transcriptional repressors or chromatin remodelers (Table 1)[34-36]. However, a few studies have reported MBPs in GC (Table 1). Mutations in *MBD4* have been found in gastric tumors in association with microsatellite instability[37,38]. *MBD4* encodes a protein that interacts with the mismatch repair protein hMLH1. Therefore, it has been postulated that mutations in *MBD4* may result in mismatch repair deficiency[30].

The processes of DNA methylation and histone modification often involve dynamic interactions that either reinforce or inhibit epigenetic changes. Thus, histone modification can also alter chromatin remodeling, and this is a possible mechanism for decreased gene expression[39-41].

The nature of the interaction between DNA and histones, which are composed of pairs of the four core proteins H2A, H2B, H3, and H4, alters the accessibility of DNA transcription sites to RNA polymerase Ⅱ and other transcription factors. The interaction between histones and DNA is thought to be under epigenetic control, because specific amino acid residues on specific histone core proteins are subjected to post-translational modifications, such as acetylation, methylation, phosphorylation, ubiquitination, sumoylation, proline isomerization, and ADP ribosylation[42,43]. Histone acetylation and methylation are the only modifications that have been clinically associated with pathological epigenetic disruption in cancer cells[44]. In this review, we focus on histone methylation modifications.

Histones can be mono-, di-, or trimethylated at lysine and arginine residues by histone methyltransferases (HMTs) or demethylated by histone demethylases (HDTs). Depending on the residue and the level of methylation, the chromatin may be transcriptionally active or inactive. In general, trimethylation at H3K4 and H3K36 or monomethylation at H3K27, H3K9, H4K20, H3K79, and H2BK5 is associated with transcriptional activation. In contrast, trimethylation at H3K27, H3K9, and H4K20 or monomethylation at H3K27, H3K9, H4K20, H3K79, and H2BK5 is associated with transcriptional repression[44].

A growing number of studies have analyzed the HMTs and HDMs in tumor cells, whereas few genes involved in histone methylation activity have been described for GC (Table 1). EZH2, an HMT that plays a role in trimethylation of H3K27 and leads to silencing of important genes in carcinogenesis, is overexpressed in several types of cancer, including GC[45,46]. Cai *et al*[47] reported that EZH2 plays an important role in the multistep process of intestinal-type GC. In addition, Fujii *et al*[48] demonstrated that silencing of *EZH2* by siRNA resulted in a lower H3K27me3 protein level in GC cells.

Table 1 Methylation machinery in gastric cancer

Gene	Function	Alteration in cancer	Ref.
DNMT1	Maintenance of methylation Repression of transcription	Upregulation Mutation	Kanai *et al*[93] Fang *et al*[94] Ding *et al*[95] Yang *et al*[96] Mutze *et al*[97]
DNMT3A	*De novo* methylation during embryogenesis Imprint establishment Repression	Upregulation Mutation	Ding *et al*[95] Fan *et al*[98] Yang *et al*[96]
DNMT3B	*De novo* methylation during embryogenesis Repeat methylation Repression	Upregulation Mutation	Ding *et al*[95] Su *et al*[99] Hu *et al*[100] Yang *et al*[96]
MeCP2	Transcription repression	Upregulation Mutation	Wada *et al*[101]
MBD1	Transcription repression	Upregulation Mutation	-
MBD2	Transcription repression DNA demethylase	Downregulation Mutation	Kanai *et al*[102]
MBD3	Transcription repression, but requires MBD2 to recruit it to methylated DNA	Upregulation Mutation	-
MBD4	Transcription repression DNA repair Glycosylase domain, repair of deaminated 5-methyl C	Downregulation Mutation	Pinto *et al*[38] D'Errico *et al*[37]
Kaiso	Transcription repression	Upregulation	Ogden *et al*[103]
G9a	Histone methyltransferase	Gene Repression	Lee *et al*[104]
RIZ1	Histone methyltransferase	Underexpression	Oshimo *et al*[105]
PRDM2		Mutation	Pan *et al*[106]
SUZ12	Histone methyltransferase	Upregulation	Yoo *et al*[107]
BMI1	Histone methyltransferase	Upreguletion	Liu *et al*[108] Xiao *et al*[109] Lu *et al*[110] Zhang *et al*[111] Li *et al*[112]
EVI1	Histone methyltransferase	Chromosomal rearrangement	Takahata *et al*[113]
EZH2	Histone methyltransferase	Amplification Upregulation Mutation	Mattioli *et al*[114] Varambally *et al*[115] Fujii *et al*[48] Cai *et al*[47] Choi *et al*[46] Zhou *et al*[116]
NSD2/MMMSET	Histone methyltransferase	Upregulation Translocation	Hudlebusch *et al*[117]
SUV39H1 -2	Histone methyltransferase	Polymorphism	Li *et al*[84]
LSD1/BHC110	Histone demethylase	Downregulation	Magerl *et al*[118]
JARID1A-D	Histone demethylase	Upregulation Inactivation	Zeng *et al*[51]
JMJD2A *JHDM3A*	Histone demethylase	Mutation Upregulation	Li *et al*[119]
JMJD1A-C	Histone demethylase	Downregulation	Katoh *et al*[120]

DNMT: DNA methyltransferase; *EVH1*: Domain containing 1; *EZH2*: Enhancer of zest homolog2; *JARID*: Jumonji, AT-rich interactive-domain; *JHDM*: JmjC domain-containing histone demethylase 1; *JMJD*: Jumonji domain containing 2; *LSD1*: Lysine specific demethylase; *MBD*: Methyl-CpG-binding domain; *NSD2*: Nuclear receptor-binding SET-domain protein 2; *PRMT*: Protein arginine methyltransferase 1; *RIZ1*: Retinoblastoma protein-interacting zinc finger 1; *SUV39H*: Suppressor of variation 3-9 homolog.

Among the HDTs, RBP2 is a newly identified member of the JARID family of proteins, and RBP2 specifically targets tri- and dimethylated H3K4 for demethylation in cancer[49,50]. Zeng *et al*[51] reported that *RBP2* is overexpressed in GC and suggested that HDT inhibition by targeting RBP2 may be an anticancer strategy.

DNA METHYLATION

DNA methylation contributes to cancer mainly through DNA hypo- or hypermethylation. DNA hypomethylation, which refers to the loss of DNA methylation, affects chromosomal stability and increases aneuploidy[52]. DNA hypermethylation, which refers to the gain of methylation at a locus originally unmethylated, usually results in stable transcriptional silencing, which functions in regulating gene expression[53,54].

Global DNA hypomethylation is usually considered one of the hallmarks of cancer cells, because aberrant hypermethylation-vulnerable genes are overlapped by

Table 2 Aberrant DNA methylation in gastric cancer

Gene	Role	Aberrant methylation	Ref.
ABCB1	Multidrug resistance	Hyper	Poplawski *et al*[121], Tahara *et al*[122], Lee *et al*[123]
ADAM23	Tissue cell invasion and metastasis	Hyper	Takada *et al*[124], Watanabe *et al*[125], Kim *et al*[126]
ALDH2	Oxidative pathway of alcohol metabolism	Hypo	Balassiano *et al*[127]
APC	Tissue cell invasion and metastasis Signal transduction	Hyper	Bernal *et al*[128], Ksiaa *et al*[63], Shin *et al*[69], Geddert *et al*[129]
ARPC1B (*p41ARC*)	Cell morphology	Hyper	Maekita *et al*[130], Shin *et al*[69]
BNIP3	Apoptosis	Hyper	Murai *et al*[131], Hiraki *et al*[132], Sugita *et al*[133]
BRCA1	DNA repair	Hyper	Bernal *et al*[128], Ryan *et al*[134]
CAV1	Tissue cell invasion and metastasis	Hyper	Yamashida *et al*[135]
CDH1	Tissue invasion and metastasis	Hyper	Leal *et al*[136], Bernal *et al*[136], Borges *et al*[61], Tahara *et al*[122], Al-Moundhri *et al*[137], Balassiano *et al*[127]
CHFR	Cell cycle regulation	Hyper	Oki *et al*[138], Hiraki *et al*[139], Hu *et al*[140]
DAPK	Apoptosis	Hyper	Bernal *et al*[128], Zou *et al*[74], Hu *et al*[140], Tahara *et al*[122], Sugita *et al*[133]
FHIT	Apoptosis	Hyper	Leal *et al*[136], Bernal *et al*[128]
FLNC	Cell morphology	Hyper	Kim *et al*[126], Shi *et al*[141]
GATA4/5	Transcriptional factor	Hyper	Akiyama *et al*[142], Wen *et al*[143],
HAND1	Cell differentiation	Hyper	Maekita *et al*[130], Shin *et al*[69], Shi *et al*[141]
HRAS	Signal transduction	Hypo	Fang *et al*[144], Luo *et al*[145]
IGFBP3	Cell cycle regulation	Hyper	Gigek *et al*[146], Ryan *et al*[134], Chen *et al*[147]
LOX	Tissue cell invasion and adhesion	Hyper	Maekita *et al*[130], Shin *et al*[69], Tamura *et al*[148]
MGMT	DNA repair	Hyper	Bernal *et al*[128], Hibi *et al*[149], Ksiaa *et al*[63]; Zou *et al*[74], Schneider *et al*[14], Hiraki *et al*[139], Balassiano *et al*[127], Shi *et al*[141]
MLF1	Cell differentiation	Hyper	Watanabe *et al*[125], Shi *et al*[141], Yamashita *et al*[135]
MLH1	DNA repair	Hyper	Bernal *et al*[128], Poplawski *et al*[121], Hiraki *et al*[139], Kim *et al*[150], Shin *et al*[58]
MOS	Cell cycle regulation	Hypo	Shin *et al*[58]
MTHFR	DNA synthesis DNA repair DNA methylation	Hypo	Balassiano *et al*[127]
MYC	Cell cycle regulation	Hypo	Fang *et al*[144], Luo *et al*[145]
P14ARF	Cell cycle regulation Apoptosis Cell differentiation	Hyper	Balassiano *et al*[127], Geddert *et al*[129]
P16	Cell cycle regulation	Hyper	Ksiaa *et al*[63], Dong *et al*[151], Zou *et al*[74], Shin *et al*[69], Hu *et al*[140], Ryan *et al*[134], Geddert *et al*[129], Balassiano *et al*[124], Al-Moundhri *et al*[137], Shin *et al*[58]
PRDM5	Cell differentiation	Hyper	Watanabe *et al*[125], Shu *et al*[152]
RAR-beta 2	DNA binding Activation transcription	Hyper	Bernal *et al*[128], Ksiaa *et al*[63]
RASSF1A/RASSF2	DNA repair Cell cycle regulation	Hyper	Zou *et al*[74], Guo *et al*[153], Shin *et al*[58]
RORA	Cell differentiation	Hyper	Watanabe *et al*[125], Yamashida *et al*[131]
RPRM	Cell cycle regulation	Hyper	Bernal *et al*[128], Schneider *et al*[14]
RUNX3	Signal transduction	Hyper	Bernal *et al*[128], Sakakura *et al*[154], Lee *et al*[104], Zou *et al*[74], Hiraki *et al*[139], Tamura *et al*[148], Hu *et al*[140], Fan *et al*[155], Al-Moundhri *et al*[137]
SHP1	Signal transduction	Hyper	Bernal *et al*[128], Ksiaa *et al*[63],
TERT	Cell senescence	Hyper	Kang *et al*[67], Wang *et al*[75], Gigek *et al*[77]
TFF1	Repair gene	Hyper	Carvalho *et al*[156], Ryan *et al*[134]
THBD	Inflammation response	Hyper	Maekita *et al*[130]; Shin *et al*[69]
TWIST1	Cell differentiation	Hyper	Kang *et al*[67], Schneider *et al*[14]

ABCB1: ATP-binding cassette, sub-family B (MDR/TAP), member 1; *ADAM23*: ADAM metallopeptidase domain 23; *ALDH2*: Aldehyde dehydrogenase 2 family (mitochondrial); *APC*: Adenomatous polyposis coli; *ARPC1B* (*p41ARC*): Actin related protein 2/3 complex, subunit 1B, 41kDa; *BNIP3*: Adenovirus E1B 19kDa interacting protein 3; *BRCA1*: Breast cancer 1 gene; *CAV1*: Caviolin 1; *CDH1*: Cadherin 1; *CHFR*: Checkpoint with forkhead and ring finger domains; *DAPK*: Dapk death associated protein kinase; *FHIT*: Fragile histidine triad gene; *FLNC*: Filamin C, gamma; GATA4/5: GATA binding protein 4/5; GSTP1: Glutathione S-transferase pi 1; *HAND1*: Heart and neural crest derivatives expressed 1; *HRAS*: v-Ha-ras Harvey rat sarcoma viral oncogene homolog; IGFBP3: Insulin-like growth factor; binding protein 3; *LOX*: Lysyl oxidase; *MGMT*: O-6-methylguanine-DNA methyltransferase; *MLF1*: Myeloid leukemia factor 1; *MLH1*: MutL homolog 1; *MOS*: Moloney murine sarcoma viral oncogene homolog; *MTHFR*: Methylenetetrahydrofolate reductase (NADPH); *MYC*: v-myc myelocytomatosis viral oncogene homolog (avian); *P14ARF*: Cyclin-dependent kinase inhibitor 2A; *P16*: Cyclin-dependent kinase inhibitor 2A; *PRDM5*: PR domain containing 5; *RAR-beta 2*: Retinoic acid receptor β 2 gene; *RASSF1A/RASSF2*: Ras association (RalGDS/AF-6) domain family member 1/member 2; *RORA*: RAR-related orphan receptor A; *RPRM*: TP53 dependent G_2 arrest mediator candidate; *RUNX3*: Runt-related transcription factor 3; *SHP1*: Hematopoietic cell-specific protein-tyrosine phosphatase; *TERT*: Telomerase reverse transcriptase; *TFF1*: Trefoil factor 1; *TFPI2*: Tissue factor pathway inhibitor 2; *THBD*: Thrombomodulin; *TWIST1*: Twist homolog 1.

genes targeted by hypomethylation[55,56]. Compare *et al*[57] suggested that global DNA hypomethylation may be implicated in GC associated with *H. pylori* infection at an early stage. At the individual gene level, DNA hypomethylation is often associated with activation of proto-oncogenes.

In GC, few studies have shown promoter hypomethylation associated with the activation of proto-oncogenes (Table 2). In particular, Shin *et al*[58] reported that the hypomethylation of the *MOS* promoter in GC was associated with tumor invasion, lymph node metastasis, and the diffuse type. A number of genes involved in cell cycle regulation, tumor cell invasion, DNA repair, chromatin remodeling, cell signaling, transcription, and apoptosis are known to be silenced by hypermethylation in GC (Table 2).

Multiple reports have been published regarding gene hypermethylation in both intestinal and diffuse types of GC. Interestingly, the methylation profile differs between the intestinal and diffuse types of GC[54].

The epithelial cadherin gene *CDH1*, which is a well-studied gene involved in cancer, is downregulated in gastric tumors and is hypermethylated more frequently in the diffuse type than in the intestinal type of GC. Loss of *CDH1* during tumor progression has led to the notion that this is a tumor suppressor gene[59,60]. In addition, mapping of the *CDH1* promoter has revealed a positive association between hypermethylation and older age, as well as a significant correlation between DNA hypermethylation and the A allele of the -160 C→A polymorphism. The A allele has been described to increase the risk of developing GC in association with the methylation status[61]. Unlike the *CDH1* gene, the *P16* gene is hypermethylated mainly in the intestinal type of GC[54,62,63]. This epigenetic mark was recently associated with tumor location and *H. pylori* infection in GC[64].

Other studies have also described a number of genes that are silenced by hypermethylation in association with *H. pylori* or EBV infection: *APC*, *SHP1*, *p14*, and *CDH1*[63,65-67]. According to Chan *et al*[68], the eradication of *H. pylori* infection significantly reduces the methylation index of the *CDH1* promoter. In contrast, it has been shown that a portion of the aberrant DNA methylation induced by *H. pylori* infection may persist even after the infection has disappeared[69,70]. Shin *et al*[58] observed that the methylation levels in *MOS* remained significantly increased in patients with previous *H. pylori* infection compared with *H. pylori*-negative subjects.

Moreover, hypermethylation of several gene promoters has also been observed in the premalignant stages of GC, suggesting that aberrant methylation occurs early during gastric carcinogenesis[59,71-74]. For example, the methylation levels of the catalytic subunit of the telomerase gene (*hTERT*) promoter are increased during gastric carcinogenesis. Wang *et al*[75] reported that the *hTERT* promoter was more methylated in GC than in precancerous lesions and non-neoplastic gastric tissues. Therefore, it has been suggested that the degree of methylation of the *hTERT* promoter may be useful in the early diagnosis of GC and/or may have an impact on the anti-telomerase strategy for cancer therapy. Other studies, however, showed that methylation of the *hTERT* promoter and resultant gene expression were opposite to the general model of regulation by DNA methylation, which is usually dependent on the CpG islands studied[76,77].

Recently, aberrant hypermethylation of the newly associated metastatic suppressor gene *RECK* was found to be associated with GC development and may also be useful for early diagnosis and treatment[78]. These abovementioned findings lead to the possibilities that epigenetic alterations may also occur at different stages of gastric tumorigenesis.

HISTONE METHYLATION

Histone modifications leading to gene expression alterations have been described in several cancer types, but the methylation status of chromatin is still unclear for GC. Using the ChIP-on-chip technique, Zhang *et al*[79] identified candidate genes with significant differences in H3K27me3 in GC samples compared to adjacent non-neoplastic gastric tissues. These genes included oncogenes, tumor suppressor genes, cell cycle regulators, and genes involved in cell adhesion. Moreover, these investigators demonstrated that higher levels of H3K27me3 produce gene expression changes in *MMP15*, *UNC5B,* and *SHH*.

In 2011, Kwon *et al*[80] showed that *LAMB3* and *LAMC2* were overexpressed in GC samples in comparison with non-neoplastic adjacent tissue samples. Furthermore, these researchers demonstrated that overexpression of these genes was a result of the enrichment of H3K4me3 in the gene promoter. Using immunohistochemistry, Park *et al*[81] showed that higher levels of H3K9me3, which is a repressive mark, was associated with higher T stage, lymphovascular invasion, and recurrence in gastric tumors. They also observed that the level of H3K9me3 was correlated with patient survival, because stronger methylation corresponded to a worse prognosis and intermediate methylation to an intermediate prognosis.

Taken together with results from previous studies, these results have suggested that histone methylation results in a worse prognosis by inactivating certain tumor suppressor genes[82,83]. Moreover, Li *et al*[84] used GC cell lines to demonstrate that the PRC1 member CBX7 initiated trimethylation of H3K9 at the *P16* locus through recruitment and/or activation of the HMT SUV39H2 to the target locus. This finding links two repressive epigenetic landmarks, H3K9me3 formation and PRC1 binding within the silenced domains in euchromatin, and builds up a full pathway for epigenetic inactivation of *P16* by histone modifications.

Recently, Angrisano *et al*[85] reported that *H. pylori* infection is followed by activation of *iNOS* gene expression, chromatin changes at the *iNOS* promoter (including decreased H3K9 methylation and increased H3K4 methylation), and selective release of MBD2 from the *iNOS*

promoter in a GC cell line.

METHYLATION INHIBITOR DRUGS

The silencing of cancer-related genes by DNA methylation and chromatin modification are reversible and may represent a viable epigenetic therapeutic target. In the last decade, drugs that modify chromatin or DNA methylation status have been used alone or in combination in order to affect therapeutic outcomes[86]. Specially, cytosine analogs (5-azacytidine and 5-aza-2'- deoxycytidine) are powerful mechanism-based inhibitors of DNA cytosine methylation. These cytosine analogs are incorporated into the DNA of replicating cells after the drugs have been metabolized to the appropriate dNTP. After incorporation into the DNA, the analogs interact with DNA methyltransferases to form covalent intermediates, and this interaction inhibits DNA methylation in subsequent rounds of DNA synthesis[87]. Both drugs have been approved by the US Food and Drug Administration for use in hematological malignancy treatment[88].

In GC, surgery remains the primary curative treatment for gastric tumors. Currently, adjuvant and neoadjuvant therapies are accepted[89]; however, so-called epigenetic therapy has not yet been used in treatment of GC patients.

In the past few years, epigenetic screening techniques using treatment with a demethylating agent have been developed to identify genes with epigenetic aberrations in GC cell lines. Zheng *et al*[90] treated a GC cell line with 5-aza-2'-deoxycytidine and performed DNA methylation array analysis of these cells with six normal mucosal samples from healthy patients. These results revealed 82 hypermethylated gene promoters. These authors investigated 15 candidate genes by methylation-specific PCR and confirmed five highly methylated promoters: *BX141696*, *WT1*, *CYP26B1*, *KCNA4,* and *FAM84A*. All of these, except *FAM84A*, also showed DNA hypermethylation in serum of GC patients, suggesting that serum DNA offers a readily accessible bioresource for methylation analysis.

A similar study conducted by Jee *et al*[91] described 11 selected genes and validated the genes in three GC cell lines and in non-neoplastic gastric tissue by bisulfate sequencing. Differential DNA hypermethylation was observed in *GPX1*, *IGFBP6*, *IRF7*, *GPX3*, *TFPI2,* and *DMRT1* promoter regions in GC cells but not in non-neoplastic tissues. Moreover, a poor survival rate was observed in those individuals with higher methylation status at the *TFPI2* gene. *TFPI2* is a serine protease inhibitor, which negatively regulates the enzymatic activities of trypsin, plasmin, and a tissue factor complex. Therefore, it has been proposed that this gene inactivation may be implicated in human carcinogenesis and metastasis[92].

CONCLUSION

In summary, aberrant DNA methylation and histone modification play a crucial role in gastric carcinogenesis. Thus, the recognition of the methylation machinery, genes with aberrant methylation status, and histone methylation levels in gastric carcinogenesis exemplified in this review allow us to contemplate the possibility of dealing with the aforementioned oncological issue in a new way that may have a significant impact on the therapy and management of GC.

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