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 sequence of DNA, and these changes lead to transcriptional activation or silencing of the gene. Interestingly, epigenetic modifications of DNA can also increase mutagenesis and influence the interactions between DNA and carcinogens and ultraviolet light[11]. Epigenetic modifications play a central role in gastric car-
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[5]. However, methylation in gene bodies does not block transcription and is sometimes associated with active transcription[10]. Methylation status is controlled by DNA methyltransferases (DNMT1, DNMT3A, and DNMT3B)[11]. 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[12]. Another DNA methyltransferase family member, DNMT3L, interacts with DNMT3A and DNMT3B to facilitate methylation of retrotransposons[13]. 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[14]. In particular, DNMT1 overexpression has been associated with EBV infection in GC[15-17].

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[18]. 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[19,20]. MBD family proteins (MeCP2, MBD1, MBD2, MBD3 and MBD4) bind methylated CpG (5mCpG) through a conserved protein motif called the methyl-CpG binding domain[21,22]. 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[23] 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 SmtCpG[24,25].

In cancer, the roles of MBPs are related to their functions as transcriptional repressors or chromatin remodelers (Table 1)[26,27]. 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[28,29]. 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 repress or inhibit epigenetic changes. Thus, histone modification can also alter chromatin remodeling, and this is a possible mechanism for decreased gene expression[31,32].

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[33,34]. Histone acetylation and methylation are the only modifications that have been clinically associated with pathological epigenetic disruption in cancer cells[35]. 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 (HDMTs). 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[36].

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[37,38]. Cai et al[39] reported that EZH2 plays an important role in the multistep process of intestinal-type GC. In addition, Fuji et al[40] 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                    | Upregulation         | Kanai et al [80]  |
|            | Repression of transcription                    | Mutation             | Fang et al [89]   |
|            |                                                |                      | Ding et al [89]   |
|            |                                                |                      | Yang et al [89]   |
|            |                                                |                      | Mutze et al [87]  |
|            |                                                |                      | Ding et al [89]   |
|            |                                                |                      | Fan et al [89]    |
|            |                                                |                      | Yang et al [89]   |
| DNMT3A     | De novo methylation during embryogenesis       | Upregulation         | Ding et al [89]   |
|            | Imprint establishment                          | Mutation             | Su et al [96]     |
| DNMT3B     | De novo methylation during embryogenesis       | Upregulation         | Hu et al [88]     |
|            | Repeat methylation                             | Mutation             | Yang et al [89]   |
| McCP2      | Transcription repression                       | Upregulation         | Wada et al [80]   |
| MBD1       | Transcription repression                       | Upregulation         | -                 |
| MBD2       | Transcription repression DNA demethylase       | Downregulation       | Kanai et al [80]  |
| MBD3       | Transcription repression, but requires MBD2 to recruit it to methylated DNA | Downregulation       | -                 |
| MBD4       | Transcription repression DNA repair Glycosylase domain, repair of deaminated 5-methyl C | Downregulation       | -                 |
| Kaiso      | Transcription repression                       | Upregulation         | Ogden et al [80]  |
| G9a        | Histone methyltransferase                      | Gene Repression      | Lee et al [80]    |
| PRDM2      | Histone methyltransferase                      | Underexpression      | Oshimo et al [85] |
| SLZI2      | Histone methyltransferase                      | Uproegulation        | Pan et al [96]    |
| BMI1       | Histone methyltransferase                      | Uproegulation        | Yoo et al [87]    |
|            |                                                |                      | Liu et al [88]    |
|            |                                                |                      | Xiao et al [96]   |
|            |                                                |                      | Lu et al [96]     |
|            |                                                |                      | Zhang et al [81]  |
|            |                                                |                      | Li et al [92]     |
|            |                                                |                      | Takahata et al [92]|
|            |                                                |                      | Mattioli et al [84]|
|            |                                                |                      | Varambally et al [85]|
|            |                                                |                      | Fujii et al [89]  |
|            |                                                |                      | Cai et al [90]    |
|            |                                                |                      | Chok et al [90]   |
|            |                                                |                      | Zhou et al [80]   |
|            |                                                |                      | Hudlebusch et al [87]|
| NSD2/MMMSET| Histone methyltransferase                      | Uproegulation         | -                 |
| SLIV38H1-2 | Histone methyltransferase                      | Translocation        | Li et al [86]     |
| LSD1/BHC110| Histone demethylase                            | Polymorphism         | Magee et al [80]  |
| JARID1A-D  | Histone demethylase                            | Downregulation       | Zeng et al [89]   |
| JARID2A    | Histone demethylase                            | Upregulation         | Li et al [88]     |
| JARID3A    | Histone demethylase                            | Uproegulation        | -                 |
| JARID3A-C  | Histone demethylase                            | Downregulation       | -                 |

DNMT: DNA methyltransferase; EVH1: Domain containing 1; EZH2: Enhancer of zeste homolog2; JARID: Jumonji, AT-rich interactive-domain; JMJD: 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; SLIV38H: 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 [84,85]. Zeng et al [81] 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 [32]. 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 [33,34].

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.                  |
|----------|-----------------------|----------------------|-----------------------|
| ABCR1    | Multidrug resistance  | Hyper                | Poplawski et al (223) |
| ADAM23   | Tissue cell invasion and metastasis | Hyper | Takada et al (224), Watanabe et al (225), Kim et al (226) |
| ALDH2    | Oxidative pathway of alcohol metabolism | Hyper | Balassiano et al (227) |
| APC      | Tissue cell invasion and metastasis | Hyper | Bernal et al (228), Ksiaa et al (229), Shin et al (230), Geddert et al (230) |
| ARPC1B (p41ARC) | Cell morphology | Hyper | Maekita et al (231), Shin et al (232) |
| BNNP3    | DNA repair           | Hyper                | Murai et al (233), Hiraki et al (234), Sugita et al (235) |
| BRCA1    | DNA repair           | Hyper                | Bernal et al (236), Ryan et al (237) |
| CAV1     | Tissue cell invasion and metastasis | Hyper | Yamashita et al (238) |
| CDH1     | Tissue invasion and metastasis | Hyper | Leal et al (239), Bernal et al (240), Borges et al (241), Takara et al (242) |
| CHFR     | Cell cycle regulation | Hyper                | Oki et al (243), Hiraki et al (244), Hu et al (245) |
| DAPK     | Apoptosis            | Hyper                | Bernal et al (246), Zou et al (247), Hu et al (248) |
| FHT      | Apoptosis            | Hyper                | Leal et al (249), Bernal et al (250) |
| FLNC     | Cell morphology      | Hyper                | Kim et al (251), Shi et al (252) |
| GATA4/5  | Transcriptional factor | Hyper | Akiyama et al (253), Weng et al (254) |
| HAND1    | Cell differentiation | Hyper                | Maekita et al (255), Shin et al (256), Shi et al (257) |
| HRAS     | Signal transduction  | Hyper                | Fang et al (258), Luo et al (259) |
| IGBP3    | Cell cycle regulation | Hyper | Gijek et al (260), Ryan et al (261), Chen et al (262) |
| LOX      | Tissue cell invasion and adhesion | Hyper | Maekita et al (263), Shin et al (264), Tamura et al (265) |
| MGMT     | DNA repair           | Hyper                | Bernal et al (266), Hibi et al (267), Ksiaa et al (268), Zou et al (269) |
| MLF1     | Cell differentiation | Hyper                | Schneider et al (270), Hiraki et al (271), Shi et al (272) |
| MLH1     | DNA repair           | Hyper                | Watanabe et al (273), Shi et al (274), Yamashita et al (275) |
| MOS      | Cell cycle regulation | Hyper                | Bernal et al (276), Poplawski et al (277), Hiraki et al (278), Kim et al (279) |
| MTHFR    | DNA synthesis        | Hyper                | Shin et al (280) |
| MYC      | Cell cycle regulation | Hyper                | Balassiano et al (281), Geddert et al (282) |
| PI4ARF   | Cell cycle regulation | Hyper                | Fang et al (283), Luo et al (284) |
| P16      | Cell cycle regulation | Hyper                | Balassiano et al (285), Geddert et al (286) |
| PRDM5    | Cell differentiation | Hyper                | Watanabe et al (287), Shi et al (288) |
| RAR-beta 2 | DNA binding          | Hyper                | Bernal et al (289), Ksiaa et al (290) |
| RASSF1A/RASSF2 | DNA repair | Hyper                | Zou et al (291), Guo et al (292), Shin et al (293) |
| RORA     | Cell cycle regulation | Hyper                | Watanabe et al (294), Yamashida et al (295) |
| RPRM     | Cell cycle regulation | Hyper                | Bernal et al (296), Schneider et al (297) |
| RUNX3    | Signal transduction  | Hyper                | Bernal et al (298), Sasaki et al (299), Lee et al (300), Zou et al (301), Hiraki et al (302), Tamura et al (303), Hu et al (304), Fan et al (305) |
| SHP1     | Signal transduction  | Hyper                | Bernal et al (306), Ksiaa et al (307) |
| TERT     | Cell senescence      | Hyper                | Kang et al (308), Wang et al (309), Gijek et al (310) |
| TFF1     | Repair gene          | Hyper                | Carvalho et al (311), Ryan et al (312) |
| THBD     | Inflammation response| Hyper                | Maekita et al (313), Shin et al (314) |
| THIST1   | Cell differentiation | Hyper                | Kang et al (315), Schneider et al (316) |

ARCB1: 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; BNNP3: Adenovirus EIB 19kDa interacting protein 3; BRCA1: Breast cancer 1 gene; CAV1: Cavin 1; CDH1: Cadherin 1; CHFR: Checkpoint with forkhead and ring finger domains; DAPK: Dapk death associated protein kinase; FHT: 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; IGBP3: 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; MOG: Moloney murine sarcoma viral oncogene homolog; MTHFR: Methylenetetrahydrofolate reductase (NADPH); MYC: v-myc myelocytomatosis viral oncogene homolog (avian); PI4ARF: Cyclin-dependent kinase inhibitor 2A; PI6: Cyclin-dependent kinase inhibitor 2A; PRDM5: Protein domain containing 5; RAR-beta 2: Retinoic acid receptor β 2 gene; RASSF1A/RASSF2: Ras association (RasGDS/AF-6) domain family member 1/member 2; RORA: RAR-related orphan receptor A; RPRM: TP53 dependent G; arrest mediator candidate; RUNX3: Runx-related transcription factor 3; SHP1: Hematopoietic cell-specific protein-tyrosine phosphatase; TERT: Telomerase reverse transcriptase; TFF1: Trefoil factor 1; TFF2: Tissue factor pathway inhibitor 2; THBD: Thrombomodulin; THIST1: Twist homolog 1.
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genes targeted by hypomethylation\cite{53,54}. Compare et al\cite{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\cite{59} 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*\cite{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\cite{10,60}. 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\cite{55}.

Unlike the *CDH1* gene, the *P16* gene is hypermethylated mainly in the intestinal type of *GC*\cite{54,62,63}. This epigenetic mark was recently associated with tumor location and *H. pylori* infection in *GC*\cite{54}.

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*\cite{53,54,55,56-57}. According to Chan et al\cite{59}, 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\cite{59,70}. Shin et al\cite{59} 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\cite{59,71-72}. For example, the methylation levels of the catalytic subunit of the telomerase gene (*hTERT*) promoter are increased during gastric carcinogenesis. Wang et al\cite{59} 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\cite{56,73}.

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\cite{58}. 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\cite{74} 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\cite{79} 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\cite{80} 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\cite{74,81}. Moreover, Li et al\cite{80} 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\cite{80} 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. 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. Both drugs have been approved by the US Food and Drug Administration for use in hematological malignancy treatment.

In GC, surgery remains the primary curative treatment for gastric tumors. Currently, adjuvant and neo-adjuvant therapies are accepted; 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. 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: BAX141696, WT1, CYP2B1, 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 biosource for methylation analysis.

A similar study conducted by Jee et al. 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.

**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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