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TOPIC HIGHLIGHT

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Epigenetics: An emerging player in gastric cancer

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Abstract

Cancers, like other diseases, arise from gene mutations and/or altered gene expression, which eventually cause dysregulation of numerous proteins and noncoding RNAs. Changes in gene expression, *i.e.*, upregulation of oncogenes and/or downregulation of tumor suppressor genes, can be generated not only by genetic and environmental factors but also by epigenetic factors, which are inheritable but nongenetic modifications of cellular chromosome components. Identification of the factors that contribute to individual cancers is a prerequisite to a full understanding of cancer mechanisms and the development of customized cancer therapies. The search for genetic and environmental factors has a long history in cancer research, but epigenetic factors only recently began to be associated with cancer formation, progression, and metastasis. Epigenetic alterations of chromatin include DNA methylation and histone modifications, which can affect gene-expression profiles. Recent studies have revealed diverse mechanisms by which chromatin modifiers, including writers, erasers and readers of the aforementioned modifications, contribute to the formation and progression of cancer. Furthermore, functional RNAs, such as microRNAs and long noncoding RNAs, have also been identified as key players in these processes. This review highlights recent findings concerning the epigenetic alterations associated with cancers, especially gastric cancer.

Key words: Gastric cancer; Epigenetics; DNA methylation; Histone modification; Gene expression

Core tip: The pathogenesis of gastric, or stomach cancer has long been a topic of extensive research, and these research efforts have resulted in tremendous improvements in the diagnosis and treatment of gastric cancer patients. However, research on gastric cancer has been focused on the genetic and environmental determinants of its formation and progression while the role of regulators, another important set of contributors to gastric cancer, has just begun to be elucidated. In this review, we highlight our current understanding of the epigenetic mechanisms by which gastric cancer arises and progresses and discuss future research directions.

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INTRODUCTION

Gastric cancer is the fourth most frequently occurring cancer worldwide and the second leading cause of cancer-related death[1]. The occurrence of gastric cancer varies with geographic area, with the highest incidence rate of gastric cancer in East Asia, especially South Korea, Mongolia, Japan and China. Although the mortality rate

has dramatically decreased due to improvements in endoscopy and surgical technology, the survival rate is still less than 15% once gastric cancer metastasizes.

Gastric cancer can arise from precursor lesions or *de novo* and is commonly categorized into two main subtypes, diffuse-type gastric cancer and intestinal-type gastric cancer. Research in the past decades has provided us with insights into the molecular mechanisms that drive gastric cancer tumorigenesis and progression. As in other types of cancer, genetic, epigenetic and environmental factors in combination contribute to gastric cancer tumorigenesis and progression. Previous research has mainly focused on genetic factors such as the inheritance of gastric cancer susceptibility genes and environmental factors including *Helicobacter pylori* infection, salt consumption, stress, smoking *etc*. In recent years, however, the epigenetic mechanisms governing gastric cancer have been at the center of gastric cancer research.

EPIGENETIC REGULATION OF GENE EXPRESSION

In multi-cellular organisms, different gene expression patterns determine the fates of cells, causing them to differentiate into various cell types. Therefore, it is critical to precisely coordinate the gene expression pattern based on cell types during developmental processes. Furthermore, gene expression patterns need to be maintained throughout the life span once established. Each cell appears to "memorize" the genetic information to be expressed and precisely passes this memory on to its daughter cells after cell division. This process is referred to as "epigenetic cellular memory". Dysregulation of epigenetic memory causes developmental defects, cancers and neurodegenerative diseases.

In the nucleus, DNA is packaged into a higher order structure called chromatin, the physiological template for transcription. Alteration of chromatin structure *via* the various modifications described below is the major factor that controls gene expression in a temporal and spatial manner, resulting in the establishment and maintenance of epigenetic cellular memory.

Regulation by DNA methylation

Chromatin structure is modified and altered in several layers. First of all, DNA itself is methylated, and this event mostly occurs at cytosines in CpG-rich regions. DNA methylation at promoter regions generally occludes the binding of transcription factors or recruits methyl-DNA-binding proteins, leading to the inactivation of gene expression, with few exceptions in which DNA methylation can be involved in preventing gene repression[2]. DNA methylation is a stable epigenetic mark that is inherited by offspring or daughter cells once established.

Two different classes of DNA methyltransferases (DNMTs) are responsible for establishing and maintaining DNA methylation. DNMT1 maintains DNA methylation through its substrate preference for hemimethylated DNA at CpG regions. DNMT3 family members, DNMT3A, DNMT3B and DNMT3L, are involved in establishing *de novo* DNA methylation patterns, although DNMT3L is catalytically inactive and might cause gene repression independent of DNA methylation[3].

DNA methylation was once believed to be a permanent epigenetic mark. So far, no enzyme has been discovered that directly removes the methyl group from methylcytosine. However, TET family proteins were identified to oxidize 5-methylcytosine to 5-hydroxymethylcytosine, eventually leading to the removal of the methyl group from methylcytosine[4]. TET family proteins are involved in regulating transcription during embryonic development. The tight regulation of writing and erasing methyl marks on DNA is required for proper gene expression, and the imbalance between writing and erasing is implicated in various cancers.

Regulation by histone modifications

The nucleosome, which is composed of 146 bp of DNA and a histone octamer (dimers of H2A, H2B, H3 and H4) is the fundamental repeating unit of chromatin structure and a major target of chromatin regulation[5]. Histone proteins have long flexible N-terminal tails that are subject to several covalent modifications including acetylation, methylation, phosphorylation, ubiquitylation, ADP-ribosylation, crotonylation and glutarylation[6].

The combinations of different types and locations of histone modifications, also known as histone codes, are the main determinants of gene repression or activation. Covalent modifications are regulated by a trio of writers, erasers and readers. Writers and erasers add and remove covalent modifications, respectively, while readers recognize specific modifications with specialized domains, resulting in the recruitment of transcriptional machinery or transcription-repression complexes. More detailed descriptions are given in the sections below.

Regulation by histone lysine acetylation and deacetylation

The first covalent modification identified was the acetylation of lysine (Lys or K) residues of histones by histone acetyltransferases (HATs), more specifically called histone lysine acetyltransferases (KATs). Many Lys residues of histones are involved in interacting with DNA, and this acetylation neutralizes the positive charge of Lys, leading to the weakening of the DNA-histone interaction and subsequent activation of transcription[7]. In addition, acetyllysine recruits other chromatin modifiers containing a bromodomain that recognizes an acetyllysine to activate transcription[8].

Histone deacetylases (HDACs), the erasers of acetylation, have been shown to be directly involved in cancer pathogenesis *via* transcriptional repression of tumor suppressor genes[9]. Some HDAC inhibitors are currently in use to treat certain types of cancer or in clinical trials[9].

Regulation by histone lysine methylation and demethylation

Several Lys residues of histones can also be mono-, di- or trimethylated. The different locations and levels of histone methylation add another layer of complexity to covalent modification of histones. Among histone lysine methylations, those of histone H3 Lys4 (denoted as H3K4) and histone H3 Lys27 (H3K27) are particularly interesting because H3K4 and H3K27 methylations are directly implicated in transcriptional activation and repression, respectively[10].

Methylation of H3K4 and H3K27 is catalyzed by multi-subunit protein complexes. For example, KMT2A (K-specific methyltransferase 2A, commonly called MLL), which methylates H3K4 using its SET domain, is complexed with WDR5, RBBP5 and ASH2L[11]. H3K27 is methylated by PRC2 (polycomb repressive complex 2) composed of EED, EZH2, SUZ12 and RBBP4[12].

It is not clearly understood how H3K4 or H3K27 methylation regulates transcriptional activation or repression, respectively. However, it has been shown that H3K4 methylation recruits the BAF chromatin remodeling complex *via* its chromodomain to activate transcription[13]. In regard to H3K27 methylation, another polycomb repressive complex, PRC1, recognizes trimethylated H3K27 (denoted as H3K27me3) *via* the chromodomain-containing protein CBX1 (chromobox homolog 1) and induces the compaction of chromatin, resulting in transcriptional repression, although the requirement of H3K27me3 for PRC1 function is controversial[14-16].

Because histone methylation status is critical for gene expression, the removal of histone methylation is highly regulated by several histone Lys-specific demethylases (KDMs). H3K4 is demethylated by KDM1 (commonly known as LSD1) and KDM5B (JARID1), whereas H3K27 is demethylated by KDM6A (UTX) and KDM6B (JMJD3)[10]. Because the balance between methylation and demethylation of histones is critical for coordinating gene expression, the disruption of this balance is found in many cancers.

Regulation by histone arginine methylation

Arginine (Arg or R) residues in histones are also targets for methylation. Arg methylation affects gene expression by activating or repressing transcription depending on the methylated sites[17]. Arg can be monomethylated, symmetrically dimethylated, or asymmetrically dimethylated, although the different biological consequences of symmetric *vs* asymmetric Arg dimethylation are unclear.

The methylation of Arg functions in at least two different ways. The methylation of Arg near a Lys in histones can block the Lys methylation[18]. Specifically, methylation of histone H3 Arg2 (denoted as H3R2) represses transcription by blocking H3K4 methylation, which is critical for transcriptional activation[19]. In addition, methylarginine may serve as a site-specific docking stage for methylarginine-binding proteins, which recruit other transcriptional regulators[20].

Regulation by other histone modifications and nucleosome variants

Other covalent modifications such as ubiquitylation, crotonylation and glutarylation are also involved in regulating gene expression. However, the downstream pathways of these modifications are not well studied.

A canonical nucleosome is composed of histones H3, H4, H2A and H2B. There are also several histone variants such as H3.3, H2A.Z, CENP-A and macroH2A, which are incorporated into nucleosomes with other histones to execute their specific functions. For example, histone H3.3 is not only found in transcriptionally active genes but is also involved in recruiting PRC2. H2A.Z functions in the cell cycle, and the improper incorporation of H2A.Z is implicated in various cancers[21].

Regulation by chromatin remodeling

The immediate consequence of forming a nucleosome is to limit DNA accessibility by protein factors. Therefore, cells have developed an elaborate system to remodel nucleosomes using ATP as an energy source. ATP-dependent chromatin remodeling complexes are classified into five families depending on the type of ATPase subunit of the complexes and are known as the SWI/SNF, ISWI, CHD, INO80 and SWR1 families.

Each ATP-dependent chromatin remodeling family is believed to remodel nucleosomes *via* a distinct mechanism and is involved in a distinct biological pathway, such as gene repression, gene activation, histone exchange and the DNA-damage response[22]. Due to the importance of the roles of ATP-dependent chromatin remodelers in various physiological processes, mutations and overexpression of the remodelers are often found in several cancers.

Regulation by long noncoding RNAs

The most interesting but least studied epigenetic regulator is long noncoding RNAs (lncRNAs), which are defined as transcripts that are generally longer than 200 nucleotides and do not code for proteins. Most lncRNAs are synthesized by RNA polymerase II, capped at the 5' end and polyadenylated at the 3' end[23]. Although the role of lncRNAs in chromatin regulation was first identified in X-chromosome inactivation several decades ago, the significance of lncRNAs in chromatin regulation was not fully recognized until the recent discovery that many lncRNAs interact with chromatin modifiers and directly control gene expression[24].

Although exact mechanisms of lncRNAs are not well understood, it is believed that lncRNAs function through their binding partners in several different ways[25]. They function as a scaffold for multi-subunit protein complex formation or recruit chromatin modifying complexes to a specific locus leading to transcriptional activation or repression. For example, HOTAIR (HOX antisense intergenic RNA) transcribed from a *HOXC* locus interacts with PRC2 and LSD1 *via* its 5' and 3' ends, respectively, to repress gene expression.

CANCER AND EPIGENETICS

Numerous studies have unraveled complex networks of epigenetic regulation in several types of cancer. In this section, we will highlight some of the epigenetic mechanisms that contribute to tumorigenesis and tumor progression, mainly focusing on DNA methylation, histone acetylation, histone methylation and lncRNAs.

DNA methylation in cancer

In general, cancer cells exhibit hypermethylation of the CpG islands of some genes, including tumor suppressor genes, *BRCA1* (breast cancer 1, early onset), *CDKN2A* (cyclin-dependent kinase inhibitor 2A), *MLH1* (mutL homolog 1) and *VHL* (von Hippel-Lindau tumor suppressor, E3 ubiquitin protein ligase)[26-28]. In contrast, cancer cells exhibit global hypomethylation at many genomic sequences, which can result in chromosomal instability as well as activation of proto-oncogenes[29-31].

DNA methyltransferase genes have been shown to be mutated in certain cancers. For example, *DNMT3A* gene is mutated in acute myelogenous leukemia, myeloproliferative disease and myelodysplastic syndrome[32]. In addition, the recently identified TET1 (tet methylcytosine dioxygenase 1) and TET2 (tet methylcytosine dioxygenase 2) proteins in the Tet (ten-eleven translocation) family of DNA hydroxylases are involved in DNA demethylation and found to be mutated in acute myelogenous leukemia, myeloproliferative disease, myelodysplastic syndrome and chronic myelomonocytic leukemia. Furthermore, *TET1* gene is also fused with the histone methyltransferase *MLL* (myeloid/lymphoid or mixed-lineage leukemia) gene in some cases of acute myelogenous leukemia[33,34].

Histone modifications in cancer

As described above, histone modification status is finely regulated by modification writers and erasers. Disruption of this balance can cause aberrant histone modifications, resulting in dysregulation of gene expression. In cancer cells, one of the best-established changes in histone modifications is a global decrease in the acetylation of H4K16 and trimethylation of H4K20[35]. Recent findings regarding the roles of histone modifications in various types of cancer are summarized in the sections below.

Histone acetylation modifiers in cancer

In cancer cells, mutations or changes in the expression of HATs and HDACs are frequently observed. For example, some genes that encode HATs such as CREBBP (alternatively called CBP), EP300 (p300), KAT6A (MOZ), KAT6B (MORF) and MOXD1 (MOX) have been shown to be mutated, translocated, or overexpressed in solid and hematological tumors[35-38]. In addition, altered expression of HDACs has been observed in a variety of cancers, while somatic mutations are rarely found. Moreover, the recruitment of HDACs to certain target genes *via* chimeric fusion proteins, which can occur in leukemia, has been shown to be another mechanism of gene repression[39].

In addition to HATs and HDACs, proteins called acetylation readers, which contain a bromodomain that recognizes acetylated histones and recruits other complexes, have been reported to undergo mutations or translocations in certain tumor types, suggesting that modification readers also contribute to tumorigenesis.

Histone lysine methylation writers in cancer

Histone methylation can take place at lysine, histidine or arginine residues. However, we will mainly discuss lysine and arginine methylation in this section. With the discovery of histone lysine demethylases (KDMs), the contribution of aberrant histone methylation status to tumorigenesis and cancer progression has received renewed attention in the field of cancer epigenetics in recent years.

Alteration of histone methylation status can be a consequence of translocation, amplification, deletion, overexpression or repression of histone methyltransferase or demethylase genes. The best-studied methyltransferase that undergoes chromosomal translocation is KMT2A (commonly known as MLL). This H3K4 methyltransferase is often fused with another protein, such as AFF1 (AF4/FMR2 family, member 1), ELL (elongation factor RNA polymerase Ⅱ, alternatively called ELL1), MLLT1 (myeloid/lymphoid or mixed-lineage leukemia; translocated to, 1, or ENL) or MLLT3 (myeloid/lymphoid or mixed-lineage leukemia; translocated to, 3, or AF9)[36,39,40]. MLL-fusion proteins can cause aberrant H3K4 methylation of target genes including *HOXA7* (homeobox A7) and *HOXA9* (homeobox A9)[41]. Intriguingly, several MLL-fusion proteins have been reported to recruit other histone methyltransferase such as DOT1L (DOT1-like histone H3K79 methyltransferase) in leukemia[42]. Elevated expression of another H3K4 methyltransferase, SMYD, was found in breast cancer.

In contrast, overexpression of another H3K27 methyltransferase gene, *EZH2*, has been observed in a wide variety of solid tumors and exhibits a strong association with tumor stage and aggressiveness. An inactivating mutation of *EZH2* has also been found in lymphoid, myeloid and T-cell acute lymphoblastic leukemia (T-ALL)[43]. Specifically, NOTCH1 antagonizes PRC2, thus driving the formation of T-ALL. Another histone methyltransferase that undergoes mutation, translocation or repression is the H3K36-specific methyltransferase NSD1[44,45].

Histone lysine methylation erasers in cancer

In addition to histone methyltransferases, the role of histone demethylases in cancer has been highlighted in recent studies. The activity of histone demethylases can be dysregulated by somatic mutations or changes in their expression in cancer cells. So far, somatic mutations have been found in *KDM5A* (commonly known as *JARID1A*), *KDM5C* (*JARID1C*) and *KDM6A* (*UTX*)[28,46]. Specifically, mutations in *UTX*, a histone H3K27 demethylase gene, have been found in 12 different types of cancer,

indicating a tumor-suppressive role of UTX in various cancers. This concept was supported by a recent finding showing that UTX controls the cell cycle by targeting the RB1 (Rb) protein network[47].

In contrast, the role of KDM6B (JMJD3), another H3K27 demethylase, seems to vary depending on the type of cancer. For example, JMJD3 has been shown to function in oncogene-induced senescence, suggesting a tumor-suppressive role of the protein[48]. However, upregulation of JMJD3 in metastatic prostate cancer indicates a potential role of the protein in the progression of prostate cancer[48]. In addition, overexpression of the histone H3K4 demethylase gene *KDM1A* (*LSD1*) has been associated with the recurrence of prostate cancer[49]. Furthermore, LSD1 has been identified as a positive regulator of neuroblastoma and breast tumors[50,51].

Other enzymes with altered expression in cancer include KDM2B (JHDM1B), KDM4C (JMJD2C), KDM5A (RBP2) and KDM5B (PLU1)[52-57]. JMJD2C, a member of the JMJD2 H3K9 demethylase family, has been shown to be upregulated in various tumors including breast cancer, prostate cancer, esophageal squamous cell carcinoma and desmoplastic medulloblastoma[54,55,58-60]. In addition, its potential role as an oncogene has been suggested by a recent study using immortalized mammary epithelial cells[61].

Histone lysine methylation readers in cancer

Like acetylation readers, methyllysine readers play a pivotal role in cancer. For example, ING (inhibitor of growth) family proteins, which can bind di- and trimethylated H3K4, have been found to be mutated or downregulated by the loss of heterozygosity, supporting their role as tumor suppressors in several types of cancer[62-64]. Another example of a methylated H3K4 binding protein, NUP98 (nucleoporin 98 kDa), is often fused with several subunits of histone lysine methyltransferases, thereby contributing to hematopoietic cancer[65].

Histone arginine methylation in cancer

Although histone arginine methylation has not received as much attention as lysine methylation, numerous studies have implicated the function of protein arginine methyltransferases (PRMTs) in cancers. The best-studied PRMT1 has been reported to be overexpressed and/or aberrantly spliced in various types of cancer, including breast, prostate, lung and colon cancers[66-69]. A recent study demonstrated that H4R3 methylation has a strong positive correlation with tumor stages in prostate cancer[67].

In addition to PRMT1, other PRMTs, such as PRMT2, PRMT5 and PRMT6, are overexpressed in breast, gastric, colon and lung cancers, while elevated PRMT3 activity without changes in its expression level has been reported[70-73]. Furthermore, somatic mutations in PRMT8 were found in ovarian and skin cancers. Finally, a non-PRMT family arginine methyltransferase CARM1 (coactivator-associated arginine methyltransferase 1) has been shown to be overexpressed in breast, prostate and colon cancers[74-77].

The mechanisms by which the aforementioned PRMTs contribute to tumorigenesis and metastasis have been studied by several groups. For example, PRMT1 and CARM1 are involved in the activation of WNT signaling, a well-known tumor-promoting signaling pathway[78,79]. In addition, elevated activity of PRMTs *via* the various mechanisms mentioned above can affect cell growth and migration and the tumor microenvironment.

lncRNAs in cancer

It has become clear that lncRNAs have fundamental roles in tumorigenesis and tumor progression. One of the best-studied lncRNAs is HOTAIR. HOTAIR has been shown to be overexpressed in breast and colon cancers and esophageal squamous cell carcinoma and functions *via* altering PRC2 target-gene occupancy[25,80-83]. In addition, several lncRNAs have been implicated in cancer with oncogenic functions. They include CDKN2B-AS1 (CDKN2B antisense RNA 1, or ANRIL), H19 (imprinted maternally expressed transcript), MALAT1 (metastasis associated lung adenocarcinoma transcript 1), PCAT1 (prostate cancer-associated transcript 1), PCBP2-OT1 (PCBP2 overlapping transcript 1, or TUC338), PCGEM1 (prostate-specific transcript), PRNCR1 (prostate cancer associated non-coding RNA 1) and SPRY4-IT1 (SPRY4 intronic transcript 1). These lncRNAs are often found to be upregulated in several types of cancer and exert their oncogenic effects *via* promoting cell proliferation or inhibiting apoptosis and senescence.

The mechanisms by which some of these lncRNAs execute their oncogenic functions have been uncovered. For instance, CDKN2B-AS1 functions by causing aberrant recruitment of the PRC2 complex to *CDKN2A* (cyclin-dependent kinase inhibitor 2A, or INK4A) or *CDKN2B* (cyclin-dependent kinase inhibitor 2B, or INK4B), thus suppressing their expression[84,85], whereas PCAT1 inhibits *BRCA2* (breast cancer 2, early onset) expression[86]. In contrast, other lncRNAs, such as GAS5 (growth arrest-specific 5), MEG3 (maternally expressed 3), PTENP1 (phosphatase and tensin homolog pseudogene 1) and LincRNA-p21, have been suggested to have tumor-suppressive effects[87-92]. GAS5 induces the expression of the proapoptotic protein BIRC3 (baculoviral IAP repeat containing 3, or cIAP2) and has been found to be downregulated in breast cancer[87,88], while LincRNA-p21 induces apoptosis by affecting the TP53 (p53) pathway[92].

DNA METHYLATION IN GASTRIC CANCER

As in other types of cancer, numerous studies have shown that key players in gastric cancer are regulated by changes in DNA methylation patterns at their promoter CpG islands, *i.e.*, hyper- or hypomethylation (Table 1). These genes include tumor-suppressor genes, oncogenes, and genes that are involved in tumor progression and

Table 1 Examples of epigenetic alterations found in gastric cancer

Alteration source	Expression	Alteration target	Ref.
DNA hypermethylation	Down	Signal pathway mediator genes (*ADAMTS9*, *BCL2L10*, *BCL6B*, *BNIP3*, CXCL12, *DAPK*, *DKK1*, *DKK3*, *DLL1*, *FBLN1*, *GATA4*, *HOXD10*, *LMX1A*, *OPCML*, *PCDH10*, *RELN*, *SFRP* proteins, SOCS1, *SOX17*, *TIMP3*, *VEZT*)	[100-120]
	Down	Chromatin-modifying enzyme genes (*MGMT*, *SMARCA5*)	[93,140]
	Down	MicroRNA genes (*Let-7f*, *MIR10B*, *MIR34C*, *MIR137*, *MIR155*, *MIR182*, *MIR195*, *MIR200B*, *MIR200C*, *MIR210*, *MIR212*, *MIR338*, *MIR375*, *MIR378*, *MIR429*, *MIR449*)	[127-139]
DNA hypomethylation	Up	*ALDH2*, *ASCL2*, *MTHFR*, *SULF1*, *SULF2*, *TERF2*	[122-126]
	Up	MicroRNA gene (*MIR93*)	[83]
H3/H4 hyperacetylation	Up	*MYC*	[107]
H3/H4 deacetylation	Down	*GATA*, *RND3*	[149,150]
H3 dephosphorylation	Down	*c-JUN*, *HSP70*	[151]
MicroRNA function	Down	Chromatin-modifying enzyme genes (*DNMT1*, *DNMT3A*, *DNMT3B*, *UHRF1*)	[141,142]

metastasis. In addition, recent findings demonstrating changes in the DNA methylation patterns of microRNA genes in gastric cancer patient samples have revealed more complexity in the epigenetic regulation of gastric cancer.

DNA hypermethylation in gastric cancer

Hypermethylation of CpG islands results in the silencing of neighboring genes, and promoters of tumor-suppressor genes are often methylated in gastric cancer patient samples. Widely studied genes with methylated promoters include *CDKN2A, TP53* (tumor protein p53), *MLH1, CDH1* (cadherin 1, or E-cadherin), *RUNX3* (runt-related transcription factor 3), *APC* (adenomatous polyposis coli) and *RASSF1A* (Ras association (RalGDS/AF-6) domain family member 1)[93-99]. In addition, recent studies have identified numerous hypermethylated genes encoding pro-apoptotic or anti-growth proteins (BCL2L10, BCL6B, BNIP3, DAPK and FBLN1), transcription factors (GATA4, HOXD10, LMX1A and SOX17), enzymes (KL), cell-cell interaction or migration-related proteins (ADAMTS9, OPCML, PCDH10, RELN, TIMP3 and VEZT), DNA-repair proteins (XRCC1), signaling molecules (CXCL12, DKK1, DKK3, DLL1, SFRP proteins and SOCS1), an RNA binding-protein (QKI) and others (NDRG2)[100-121].

Hypermethylation of the aforementioned genes generally promotes gastric cancer tumorigenesis and/or metastasis *via* several mechanisms. DNA methylation of tumor-suppressor genes endows gastric cells with the ability to overcome oncogene-induced senescence as well as apoptosis. For example, downregulation of DKK1 (dickkopf WNT signaling pathway inhibitor 1) and SOCS1 (suppressor of cytokine signaling 1) reactivates the WNT and STAT3 pathways, respectively[116,119,122].

DNA hypomethylation in gastric cancer

Hypomethylation causes derepression of target genes; several genes involved in tumorigenesis, progression, and metastasis of gastric cancers have been found to be hypomethylated. For example, Kwon *et al*[122] demonstrated that the promoter of *ASCL2* (achaete-scute family bHLH transcription factor 2), which encodes a basic helix-loop-helix transcription factor, shows hypomethylation in gastric cancer samples compared to normal tissues, and high expression levels of this gene are correlated with poor survival of gastric cancer patients. In addition, the promoter of the well-known oncogene *MYC* has been shown to undergo hypomethylation in gastric cancer with lymph node metastasis[123]. Yashiro *et al*[124] showed that demethylation in *TERF2* (telomeric repeat binding protein 2, or TRF2) and *ERAS* (ES cell expressed Ras) promoters causes reactivation of these genes in gastric cancer[124,125].

A recent study by Balassiano *et al*[126] reported that gastric cancer patient samples contain hypomethylated promoters of two cancer-associated genes, *ALDH2* (aldehyde dehydrogenase 2 family) and *MTHFR* (methylenetetrahydrofolate reductase). Furthermore, overexpression of *SULF1* (sulfatase 1) and *SULF2* (sulfatase 1), members of the sulfatase family, caused by promoter hypomethylation has been shown to be an independent prognostic marker for lymph node metastasis. Finally, an interesting study by Yuasa *et al*[127] showed an association between hypomethylation of blood leukocyte DNA and the risk of gastric cancer, indicating that changes in the DNA methylation pattern in non-tumor cells in addition to tumor cells themselves can be used as potential prognostic markers in gastric cancer.

MicroRNA promoter methylation in gastric cancer

MicroRNAs (miRNAs) are small noncoding RNAs that can regulate the expression of target genes at the post-transcriptional level. Because a single miRNA can target several messenger RNAs, dysregulation of miRNAs can effectively affect multiple signaling pathways leading to tumor formation and metastasis. As in other types of cancer, recent studies have identified several miRNAs as frequent targets of DNA methylation in gastric cancer (Table 1). For example, the suppression of several miRNA genes, such as *MIR137*, *MIR210*, *MIR375* or *MIR449*, *via* promoter methylation has been shown to prevent apoptosis by alleviating the miRNA-induced inhibition of pro-survival pathways such as MAPK1 (by MIR137 and MIR210) and PDK1 (by MIR375) or by inhibiting pro-apoptotic pathways (by MIR449)[128-130].

In some cases, downregulation of miRNAs *via* methylation activates tumor growth-promoting pathways such as CDK6-VEGF (by MIR195 and MIR378), c-MYC (by MIR212 and MIR429), cAMP response element (by MIR182) and MAPRE1 (by MIR10B)[28,131-133]. Thus, methylation of the aforementioned miRNAs causes overall growth of gastric cancer.

In addition to regulating gastric cancer cell survival and growth, DNA methylation of some miRNAs promotes the ability of gastric cancer cells to invade and migrate, thus increasing their metastatic potential. Examples of these include Let-7f, MIR155 and MIR338, which exert their effects by altering the expression of *MYH9* (myosin, heavy chain 9, non-muscle), *SMAD2* (SMAD family member 2) and *SSX2IP* (synovial sarcoma, X breakpoint 2 interacting protein), respectively[134-136].

Downregulation of *MIR9 via* hypermethylation in gastric cancer has also been found to increase not only proliferation but also cell migration and invasion, a prerequisite for the formation of successful metastasis, although their target genes have not been identified yet[137]. Finally, dysregulation of MIR34C can cause drug resistance by affecting MAPT (microtubule-associated protein tau)[138], and dysregulation of the *MIR200BC/429* cluster can do so by altering the expression of BCL2 (B-cell CLL/lymphoma 2) and XIAP (X-linked inhibitor of apoptosis)[139].

Hypomethylation of miRNAs has also been studied. For example, the loss of methylation at the promoter of the *MIR196* gene and upregulation of this miRNA are frequently found in primary gastric cancer, indicating the tumor-suppressive role of MIR196[83]. In addition, the upregulation of several oncogenic miRNAs such as MIR9, MIR93, MIR106B and MIR222 in gastric cancer have been reported, and their role in proliferation, anti-apoptosis and metastasis has been studied in gastric cancer cell lines[137,140,141]. However, the question of whether the upregulation of the aforementioned miRNAs is a consequence of DNA hypomethylation has yet to be answered.

Promoter methylation of chromatin-modifying enzyme genes in gastric cancer

Chromatin-modifying enzymes (CMEs) can affect the DNA methylation and histone modification status of target genes, thus causing changes in chromatin structure. Alteration at the level of CMEs can initiate several epigenetic cascades that affect diverse pathways involved in tumorigenesis and the progression and metastasis of gastric cancer.

In gastric cancer, several CMEs are also the targets of DNA methylation (Table 1). For example, Gigek *et al*[142] found that SMARCA5 (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 5), which has helicase and ATPase activity, was often downregulated in gastric cancer patient samples compared to normal tissue and as a consequence of its promoter methylation. MGMT (O-6-methylguanine-DNA methyltransferase) has also been frequently found to be absent in gastric cancer due to promoter methylation[93].

Moreover, the expression of several CMEs is regulated by miRNAs. For example, upregulation of *UHRF1* (ubiquitin-like with PHD and ring finger domains 1) expression *via* downregulation of MIR146A and MIR146B causes aberrant DNA methylation in *CDH1*, *RUNX3* and *SLIT3* (slit homolog 3) genes[143]. Furthermore, DNMT1, DNMT3A and DNMT3B proteins are downregulated *via* overexpression of *MIR200B* and *MIR200C* in gastric cancer, and this may be a cause of global DNA hypomethylation in gastric cancer cells[144].

HISTONE MODIFICATIONS IN GASTRIC CANCER

Histone modifications including acetylation, methylation, phosphorylation and ubiquitylation can directly alter gene expression. Several histone modifiers show aberrant expression patterns or mutations during tumorigenesis and cancer progression as explained above. The mechanisms by which alterations of histone modifications contribute to tumorigenesis and metastasis have been intensively studied in several types of cancer. In contrast, studies of histone modifications in gastric cancer are lacking (Table 1).

Histone-modifying enzymes in gastric cancer

Most epigenetic studies of gastric cancer have been focused on DNA methylation. Thus, scientists only recently started to investigate histone modifiers in gastric cancer. Recent findings on the role of histone modifiers in gastric cancer have shed light on the complex epigenetic mechanisms governing the development and progression of gastric cancer.

For example, histone H3K4 demethylase KDM1A (LSD1) is upregulated in some gastric cancer cells, and treatment of these cells with LSD1 inhibitors exerts cytotoxic effects as well as inhibitory effects on the migration and invasion of these cells, suggesting an important role for LSD1 in gastric cancer[145]. In addition, it has been shown that the histone deacetylase SIRT1 (sirtuin 1) plays a tumor-suppressive role in gastric cancer development *via* inhibition of NF-κB signaling and is downregulated in gastric cancer[146].

In contrast, the H3K9/K36 demethylase KDM4B (commonly called JMJD2B) was recently discovered to be a potent activator of cell proliferation as well as the epithelial-mesenchymal transition (EMT) and correlated with lymph node/distant metastasis[147,148]. Another H3K9 demethylase, JMJD1C, is also upregulated in gastric cancer. In addition, the H3K27 methyltransferase EZH2 has been shown to promote gastric cancer tumorigenesis in various model systems and exhibits significant association with patient survival as well as lymph node metastasis[149]. Furthermore, the expression of the histone lysine acetyltransferase KAT5 (TIP60) has been shown to be reduced in gastric cancer and to have a significant correlation with lymph node metastasis[150].

Genes deregulated by histone modifications in gastric cancer

Several recent studies identified genes whose expression is regulated by various histone modifications. These include the H3/H4 hyperacetylation of the *MYC* promoter *via* FOXO6/HNF4 axis, the repression of *GATA* by deacetylation of histone H3/H4 at the promoter, and the downregulation of *RND3* (*RhoE*)[107,151,152]. In addition, dephosphorylation of histone H3 serine 10 on c-*JUN* and *HSP70* genes has been shown to cause altered expression of these genes[153].

Combinatorial modifications of DNA and histones in gastric cancer

DNA methylation events are often accompanied by histone modifications and *vice versa* to tightly regulate gene expression. Several studies also discovered that the expression of several genes in gastric cancer can be regulated by DNA methylation and histone modification simultaneously. For example, Meng *et al*[154] showed that the promoter of the *CDKN2A* gene undergoes both DNA methylation and histone H3K9 dimethylation. Lee *et al*[97] showed that hypoxia silences *RUNX3*, which is known to be suppressed by DNA methylation, *via* modification of histones during the progression of gastric cancer.

Overexpression of *LAMB3* (laminin, beta 3) affects several malignant phenotypes in gastric cancer cell lines, and these genes not only undergo demethylation at CpG islands but also exhibit an increase in H3K4 trimethylation[155]. *MYO5B* (myosin VB) gene is suppressed by DNA methylation as well as histone deacetylation, causing persistent c-MET signaling in gastric cancer[156]. A study by Ma *et al*[157] demonstrated that DNA hypermethylation and histone hypomethylation of *PDX1* (pancreatic and duodenal homeobox 1) causes downregulation of this gene in gastric cancer. Finally, gene expression of PRDM5 (PR domain containing 5), a member of the kruppel-like zinc finger family, is downregulated *via* DNA methylation and H3K27 trimethylation, alleviating the cell growth suppressive effect of PRDM5[158].

LncRNAs in gastric cancer

LncRNAs, once thought to be junk in cells, have now become a center of attention in various fields from developmental biology to the study of human diseases. However, there are few studies of the role of lncRNAs in gastric cancer. Arita *et al*[159] have examined several lncRNAs previously shown to be involved in other cancers, including H19, HOTAIR and MALAT1, and showed that the plasma level of H19 was higher in gastric cancer patients than in healthy controls, raising the possibility of using lncRNA as a tumor marker in gastric cancer. Another study of H19 showed its role in the proliferation of gastric cancer cells[160].

Cao *et al*[161] compared the expression profiles of almost 10000 lncRNAs in gastric cancer and normal tissue samples and identified TUG1 (taurine upregulated 1), UCA1 (urothelial cancer associated 1), PVT1 (Pvt1 oncogene), SNHG1 (small nucleolar RNA host gene 1), LINC00152 (long intergenic non-protein coding RNA 152) and LINC00261 (long intergenic non-protein coding RNA 1261) as differentially expressed lncRNAs in gastric cancer. Studies by several groups revealed that the expression of *HOTAIR* is positively associated with gastric cancer development and plays a role in invasion and the epithelial-mesenchymal transition of gastric cancer cells[159,162,163].

DISCUSSION

Due to tremendous research efforts, it has become clear that epigenetic modification is a major contributor to the formation and metastasis of most, if not all, of cancers, including gastric cancer. Epigenetic changes including DNA methylation and histone modifications can be caused by mutations and/or altered expression of writers, erasers and readers of these modifications. These deregulated modifiers, in turn, facilitate uncontrolled expression of oncogenes and metastasis-promoting genes while keeping that of tumor- and metastasis-suppressor genes silenced.

The focus of epigenetic research in cancer has shifted from mere identification of changes in chromatin modifications to distinguishing epigenetic modifications that truly drive cancer formation from bystanders. These types of research are imperative to the design and development of effective anti-cancer therapeutic drugs. In contrast to the extensive studies on the epigenetic dysregulation of other types of cancer such as breast cancer, similar studies on gastric cancer are still lagging behind, calling for more vigorous research on this subject.

In particular, our understanding of the histone modifications in gastric cancer is very limited compared to that of other cancer types and to DNA methylation. In contrast to the few types of DNA modifications, histone modifications are more diverse, adding more layers of complexity to the epigenetic mechanisms involved in cancer. Thus, a better understanding of the network of histone modifications in gastric cancer will provide not only a complete picture of gastric cancer but also an opportunity to develop anti-gastric cancer therapeutics.

Another player whose importance in gastric cancer has only recently been identified is noncoding RNA, such as miRNAs and lncRNAs. Whereas miRNAs regulate protein-coding RNAs *via* direct binding, lncRNAs work through guiding chromatin modifiers to the target genes. Studies on the role of lncRNAs in gastric cancer have only recently begun, and we are just starting to understand their functions in gastric cancer. There is no doubt that further studies on noncoding RNAs will reveal a new paradigm in the field of gastric cancer research.

One of the remaining important needs in understanding gastric cancer is to gain insights into the diversity of epigenetic drivers in different types of gastric cancer. As in genetic modifications, the types of epigenetic changes that contribute to the formation of tumors vary depend-

ing on cancer types and subtypes even within tumors originating from the same organ. For example, a given modification contributing to intestinal-type gastric cancer may not be the key factor for diffuse-type gastric cancer development. Thus, it is crucial to understand cancer type-specific epigenetic modifications in order to develop personalized anti-gastric cancer therapeutics.

Finally, for cancer cells to grow and metastasize, they must acquire abilities to exploit surrounding stroma, emphasizing the importance of distinction between alterations in tumor cells and those in stromal cells. However, most previous studies of gastric patient samples have been performed on whole tumor tissues without separating tumor cells and surrounding stromal cells, making it hard to interpret the results. Very recently, several research groups have utilized elegant methods including fluorescence-activated cell sorting and laser capture microdissection to separate stromal cells from tumor cells.

They made the very intriguing discovery that stroma cells also undergo alterations in gene expression profiles, likely caused by epigenetic modifications. These stroma-specific changes might have been masked by the tumor cell gene expression profile if whole tumor tissue had been used. Scientists argue that targeting the tumor stroma might be a safer and more effective way to treat cancer due to the relatively stable and homogeneous features of stromal cells compared to heterogeneous and rapidly evolving tumor cells. To this end, it is imperative to accurately characterize stroma- and tumor cell-specific epigenetic changes, particularly in the case of gastric cancer.

As a final comment, the primary unmet needs for gastric cancer are the development of an accurate way to predict patients at high risk for metastasis and the generation of therapeutic drugs that effectively treat gastric cancer. This will reduce unnecessary gastrectomy, thus improving the quality of patients' life and moving us one step closer to conquering gastric cancer in the near future.

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