INTRODUCTION

After the discovery of DNA and the double helix structure, classic genetics has long assumed that the sequences of DNA determine the phenotypes of cells. DNA is packaged as chromatin in cells, with nucleosomes being the fundamental repeating unit. Four core histones (H2A, H2B, H3, and H4) form an octamer and are then surrounded by a 147-base-pair (bp) segment of DNA. Nucleosomes are separated by 10–60 bp DNA. Researchers have gradually found organisms that share the same genetic information but have different phenotypes, such as somatic cells from the same individual that share a genome but function completely differently. The term epigenetics was first proposed and established in 1942 when Conrad Waddington tried to interpret the connection between genotype and phenotype. Later, Arthur Riggs and his group interpreted epigenetics as inherited differences in mitosis and meiosis, which could explain the changes in phenotypes. They were both trying to find the link between genotype and phenotype. Epigenetics is usually referred to as a genomic mechanism that reversibly influences gene expression without altering DNA sequences. Holliday assumed that epigenetics was also mitotically and/or meiotically heritable without DNA sequence change. aberrant DNA methylation could be repaired via meiosis, but some patterns are still transmitted to offspring. This phenomenon covers a wide range of cellular activities, such as cell growth, differentiation, and disease development, and is heritable. Generally, epigenetic events involve DNA methylation, histone modification, the readout of these modifications, chromatin remodeling, and the effects of noncoding RNA. The elements involved in different modification patterns can be divided into three roles, “writer,” “reader,” and “eraser”. The “writers” and “erasers” refer to enzymes that transfer or remove chemical groups to or from DNA or histones, respectively. “Readers” are proteins that can recognize the modified DNA or histones (Fig. 1). To coordinate multiple biological processes, the epigenome cooperates with other regulatory factors, such as transcription factors and noncoding RNAs, to regulate the expression or repression of the genome. Epigenetics can also be influenced by cellular signaling pathways and extracellular stimuli. These effects are temporary and yet long-standing. Given the importance of epigenetics in influencing cell functions, a better understanding of both normal and abnormal epigenetic processes can help to understand the development and potential treatment of different types of diseases, including cancer.

The etiology of cancer is quite complicated and involves both environmental and hereditary influences. In cancer cells, the alteration of genomic information is usually detectable. Like genome instability and mutation, epigenome dysregulation is also pervasive in cancer (Fig. 2). Some of the alterations determine cell function and are involved in oncogenic transformation. However, by reversing these mutations by drugs or gene therapy, the phenotype of cancer can revert to normal. Holliday proposed a theory that epigenetic changes are responsible for tumorigenesis. The alteration of cellular methylation status by a specific methyltransferase might explain the differences in the probability of malignant transformation. In clinical settings, we noticed that although cancer patients share the same staging and grade, they present totally different outcomes. In tumor tissues, different tumor cells show various patterns of histone modification, genome-wide or in individual genes, indicating that epigenetic heterogeneity exists at a cellular level. Likewise, using molecular biomarkers is thought to be a potential method to divide patients into different groups. It is important to note that tumorigenesis is the consequence of the combined action of multiple epigenetic events. For example, the repression of tumor suppressor genes is usually caused by methylation of DNA CpG islands together with hypoacetylated and hypermethylated histones. During gene silencing, several hallmarks of epigenetic events have been
identified, including histone H3 and H4 hypoacetylation, histone H3K9 methylation, and cytosine methylation. Therefore, epigenetics enables us to investigate the potential mechanism underlying cancer phenotypes and provides potential therapy options. In this review, we focused and briefly expanded on three aspects of epigenetics in cancer: DNA methylation, histone acetylation and histone methylation. Finally, we summarized the current developments in epigenetic therapy for cancers.

DNA METHYLATION

The DNA methylation pattern in mammals follows certain rules. Germ cells usually go through a stepwise demethylation to ensure global repression and suitable gene regulation during embryonic development. After implantation, almost all CpGs experience de novo methylation except for those that are protected. Normal dynamic changes in DNA methylation and demethylation based on altered expression of enzymes have been known to be associated with aging. However, inappropreate methylation of DNA can result in multiple diseases, including inflammatory diseases, precancerous lesions, and cancer. Of note, de novo methylation of DNA in cancer serves to prevent reactivation of repressed genes rather than inducing gene repression. Because researchers have found that over 90% of genes undergoing de novo methylation in cancer are already in a repressed status in normal cells. Nevertheless, aberrant DNA methylation is thought to serve as a hallmark in cancer development by inactivating gene transcription or repressing gene transcription and affecting chromatin stability.

The precise mechanism by which DNA methylation affects chromatin structure is unclear, but it is known that methyl-DNA is closely associated with a closed chromatin structure, which is relatively inactive. Hypermethylation of promoters and hypomethylation of global DNA are quite common in cancer. It is widely accepted that gene promoters, especially key tumor suppressor genes, are unmethylated in normal tissues and highly methylated in cancer tissues. P16, a tumor suppressor encoded by CDKN2A, has been found to gain de novo methylation in ~20% of different primary neoplasms. Mutations in important and well-studied tumor-suppressive genes, such as P53 and BRCA1, are frequently identified in multiple cancers. Studies have found that the level of methylation is positively associated with tumor size. In support of this, a whole-genome methylation array analysis in breast cancer patients found significantly increased CpG methylation in FES, P2RX7, HSD17B12, and GSTM2 coincident with increasing tumor stage and size. After analysis of long-range epigenetic silencing at chromosome 2q14.2, methylation of EN1 and SCTR, the first well-studied example of coordinated epigenetic modification, was significantly increased in colorectal and prostate cancers. EN1 methylation has also been observed to be elevated by up to 60% in human salivary gland adenoid cystic carcinoma. Of note, only ~1% of normal samples exhibited EN1 CpG island hypermethylation. Therefore, the significant difference between cancer cells and normal cells makes EN1 a potential cancer marker in diagnosis. In human pancreatic...
cancer, the APC gene, encoding a regulator of cell junctions, is hypermethylated by DNMT overexpression. During an analysis of colorectal disease methylation patterns, researchers found several genes that showed significant changes between precancerous diseases and cancers, including RUNX3, NEUROG1, CACNA1G, SFRP2, IGF2, DMR0, hMLH1, and CDKN2A. In the human colon cancer cell line HCT116, hMLH1 and CDKN2A always bear genetic mutation and hypermethylation of one allele, and this leads to inactivation of key tumor suppressors. It is known that p16, p15, and pax6 are usually aberrantly methylated in bladder cancer and show enhanced methylation in cell culture. Unlike gene promoter methylation, gene body methylation usually results in increased transcriptional activity. This process often occurs in CpG-poor areas and causes a base transition from C to T. The hypermethylation of specific CpG islands in cancer tissues is informative of mutations when the gene in normal tissues is unmethylated. One representative marker is glutathione S-transferase-π (GSTP1), which is still the most common alteration in human prostate cancer. Recently, DNA methylation in cancer has generally been associated with drug resistance and predicting response to treatment. For example, MGMT (O-6-methylguanine DNA methyltransferase) hypermethylation is still the best independent predictor of response to BCNU (carmustine) and temozolomide in gliomas because hypermethylation of MGMT makes tumor cells more sensitive to treatments and is associated with regression of tumor and prolonged overall survival. Similarly, MGMT is also a useful predictor of response to cyclophosphamide in diffuse large B-cell lymphoma (Table 1).

DNA methyltransferases (DNMTs)

DNA methylation is a covalent modification of DNA and is one of the best-studied epigenetic markers. It plays an important role in normal cell physiology in a programmed manner. The best-known type of DNA methylation is methylation of cytosine (C) at the 5th position of its carbon ring (5-mC), especially at a C followed by a guanine (G), so-called CpG sites. Non-CpG methylation, such as methylation of CpA (adenine) and CpT (thymine), is not common and usually has restricted expression in mammals. CpG islands traverse ~60% of human promoters, and methylation at these sites results in obvious transcriptional repression. Meanwhile, among the ~28 million CpGs in the human genome in somatic cells, 60–80% are methylated in a symmetric manner and are frequently found in promoter regions. The process of DNA methylation is regulated by the DNA methyltransferase (DNMT)
family via the transfer of a methyl group from S-adenosyl-L-methionine (SAM) to cytosines. There are five members of the DNMT family: DNMT1, DNMT2, DNMT3a, DNMT3b, and DNMT3L. DNMT1 is responsible for the maintenance of methyl-DNA, recognizes hemimethylated DNA strands and regenerates the fully methylated DNA state of DNA during cell division. In a recent study, DNMT1 with Stella, a factor essential for female fertility, was responsible for the establishment of the oocyte methylome during early embryo development. DNMT3a and DNMT3b are regarded as de novo methylation enzymes that

### Table 1. Key regulatory factors of DNA methylation in cancer.

| Enzyme | Roles in cancer | Cancer type | Associated biological process (involved mechanism and molecules) |
|--------|----------------|-------------|---------------------------------------------------------------|
| **DNA methyltransferases** | | | |
| DNMT1: DNMT1 is responsible for maintenance of DNA methylation and is expressed at high concentrations in dividing cells to guard existing methylated sites. | Promoter | AML, CML, breast cancer, colorectal cancer, glioma, lung cancer, pancreatic cancer, gastric cancer, hepatocellular carcinoma, breast cancer, esophageal cancer, bladder cancer, thyroid cancer, ovarian cancer | Promotes EMT phenotype, cell apoptosis, cell proliferation, migration, cancer stemness, and cisplatin sensitivity ([β]-catenin, E-cadherin, PTEN, p18, p27, P21, P16, miR-124, miR-148a, miR-152, miR-185, miR-506), DNMT1 is also upregulated by Helicobacter pylori CagA |
| DNMT3a: DNMT3a methylates unmethylated DNA de novo and is required for maternal imprinting | Promoter | Cervical cancer, CML, breast cancer, gastric cancer, prostate cancer, ovarian cancer, bone cancer, testicular cancer | Promotes cell proliferation and invasion. (VEGFA, Wnt/[β]-catenin signaling, miR-182, miR-708-5p) |
| DNMT3b: DNMT3b is also responsible for de novo methylation and is required for methylation of centromeric minor satellite repeats and CGIs in inactive X chromosomes. | Promoter | CML, AML, glioma, lung cancer, breast cancer, colorectal cancer, prostate cancer, pancreatic cancer, bladder cancer, cervical cancer | Promotes cell proliferation, and invasion and the chemotherapeutic effects of cisplatin; is associated with poor prognosis (E-Cadherin, PTEN, P21, P16, miR-29b, miR-124, miR-506) |
| Methyl-CpG binding proteins | | | |
| MeCP2 | Promoter | Prostate cancer, colorectal cancer, breast cancer, gastric cancer | Promotes cell proliferation, invasion, and metastasis and the chemoradiosensitivity of cancer cells and induces an antioxidant response (E-Cadherin) |
| MBD1 | Promoter | Pancreatic cancer | Decreased expression of MeCP2 contributes to cancer development |
| MBD2 | Promoter | Lung cancer, colon cancer, breast cancer, prostate cancer | Promotes cell invasion and metastasis (p14) |
| MBD4 | Promoter | Colon cancer, breast cancer | Causes dominant negative impairment of DNA repair |
| ZBTB33 (2ZBTB33) | Promoter | Colon cancer, cervical cancer, prostate cancer, ovarian cancer, lung cancer, breast cancer, and chronic myeloid leukemia | Silencing of tumor suppressor genes, EMT, apoptosis, migration and invasion (Wnt/[β]-catenin, TGFβ, EGFR, Notch, miR-4262, miR-31) |
| ZBTB4 | Promoter | Breast cancer, Ewing sarcoma, prostate cancer, bladder cancer | Promotes cell growth and apoptosis and controls the cellular response to p53 activation, promoting long-term cell survival (miR-17-92/106b-25) |
| ZBTB38 | Promoter | Bladder cancer | Promotes cell migration and invasion (Wnt/[β]-catenin pathway) |
| UHRF1 | Promoter | Hepatocellular carcinoma, bladder cancer, bladder cancer, renal cell carcinoma, lung cancer, retinoblastoma, intrahepatic cholangiocarcinoma, colon cancer, pancreatic cancer, gastric cancer, prostate cancer, melanoma, hepatoblastoma, esophageal squamous cell carcinoma, cervical cancer, breast cancer, thyroid cancer | Promotes cell proliferation, EMT, and viability, increases hypoxia inducible factor (HIF)1α, CSCs, taxane resistance correlates with poor pathological characteristics, human papillomavirus (HPV) contributes to overexpression of UHRF1 (miR-101, miR-124, PI3K, Akt signaling pathway, MEK/ERK pathway) |
| UHRF2 | Promoter | Intrahepatic cholangiocarcinoma, hepatocellular carcinoma, colon cancer | Promotes cell migration and invasion, and is associated with lower disease-free survival |
| suppressor | Colon cancer, lung cancer, esophageal carcinoma | Low level of UHRF2 is associated with shorter overall survival, vascular invasion and poor prognosis |
| **DNA demethylases** | | | |
| TET1: TET1 is highly expressed in mouse embryonic stem cells, the inner cell mass of blastocysts, and developing PGCs. | Promoter | MLL-rearranged leukemia, AML, breast cancer, ovarian cancer, lung cancer, renal cancer | TET1-MLL fusion, cell migration, anchorage-independent growth, cancer stemness, and tumorigenicity, prevention of senescence via loss of p53, associated with a worse overall survival and sensitivity to drugs (PI3K-mTOR pathway) |
| TET2/TET3: TET2 and TET3 are present in mouse adult tissues, whereas only TET3 is present in mouse oocytes and one-cell zygotes | Promoter | MDS, AML, CML, prostate cancer, gastric cancer, breast cancer, colorectal cancer, ovarian cancer, hepatocellular carcinoma, leukemia | Promotes cell proliferation, colony formation, metastasis, is associated with reduced patient survival, pathologic stage, tumor grading, lymph node metastasis, and vascular thrombosis (caspase-4, ET2/E-cadherin/[β]-catenin regulatory loop) |
| TET2 | Suppressor | Renal cell carcinoma | Acts as an independent predictor of poor outcome |
| TET3 | Suppressor | Renal cell carcinoma | Is associated with EMT, overall survival, disease-free survival (miR-30d) |

**AML** acute myeloid leukemia, **CML** chronic myeloid leukemia, **EMT** epithelial-mesenchymal transition, **VEGFR** vascular endothelial growth factor receptor
target unmethylated CpG dinucleotides and establish new DNA methylation patterns, but they have nonoverlapping functions during different developmental stages.\textsuperscript{47,48} DNMT2 and DNMT3L are not regarded as catalytically active DNA methyltransferases. DNMT2 functions as an RNA methyltransferase, while DNMT3L contains a truncated inactive catalytic domain and acts as an accessory partner to stimulate the de novo methylation activity of DNMT3A. The DNA methyltransferase-like protein DNMT3L can modulate DNMT3a activity as a stimulatory factor.\textsuperscript{49}  

During aberrant DNA methylation, DNMTs play an important role. Compared with DNMT1 and DNMT3a, DNMT3b was significantly overexpressed in tumor tissues.\textsuperscript{50} Overexpression of DNMT1, DNMT3a, and DNMT3b has been observed in multiple cancers, including AML, CML, glioma, and breast, gastric, colorectal, hepatocellular, pancreatic, prostate, and lung cancers. In cervical cancer patients, DNMT1 was expressed in more than 70% of cancer cells, whereas only 16% of normal cells expressed DNMT1. The higher level of DNMT1 expression was also associated with worse prognosis.\textsuperscript{51} The expression of DNMT1, DNMT3a, and DNMT3b has been observed to be elevated in acute myeloid leukemia (AML) and various solid cancers. These three methyltransferases do not show significant changes in the chronic phase of chronic myeloid leukemia (CML), but they are significantly increased during progression to the acute phase in CML.\textsuperscript{52,53} Notably, downregulation of DNMTs can also lead to tumorigenesis (Table 1).  

Methyl-CpG recognition proteins  

How DNA methylation leads to gene repression has been considered in many studies. Several hypotheses have been proposed. Three methyl-CpG binding domain protein (MeCP) families can read the established methylated DNA sequences and in turn recruit histone deacetylases, a group of enzymes responsible for repressive epigenetic modifications, to inhibit gene expression and maintain genome integrity.\textsuperscript{54} The first group is methyl-CpG binding domain (MBD) proteins, including MeCP2, MBD1, MBD2, and MBD4. MeCP1 is a complex containing MBD2, the histone deacetylase (HDAC) proteins HDAC1 and HDAC2, and the RbAp46 and RbAp48 proteins (also known as RBBP7 and RBBP4).\textsuperscript{55} MBD3 is unlike the other four families members and is not capable of binding to methylated DNA but instead binds to hydroxymethylated DNA.\textsuperscript{56} The zinc-finger and BTB domain-containing protein family is the second group and comprises three structurally different proteins, KAISO (ZBTB33), ZBTB4, and ZBTB38, which bind to methylated DNA via zinc-finger motifs. The third family includes two ubiquitin-like proteins with PHD and RING finger domains, UHRF1 and UHRF2, which recognize 5-mC via RING finger-associated (SRA) domains. On the other hand, methylation of DNA can also be a barrier for certain transcription factors to bind to promoter sites such as AP-2, c-Myc, CREB, ATF, EZF, and NF-kB.\textsuperscript{57}  

As for methyl-group binding proteins, many studies have investigated their roles in various cancers, but the mechanism underlying these alterations remains unclear. MBD proteins cooperate with other proteins to regulate gene transcription.\textsuperscript{58} However, the role of MBD1 and MBD2 has not been identified in human lung or colon cancer, with only limited mutations being detected.\textsuperscript{59} Furthermore, loss of MBD1 did not show any carcinogenic effect in MBD1−/− mice.\textsuperscript{60} Compared with MBD1, MBD2 shows more effect on tumorigenesis. Deficiency of MBD2 strongly suppresses intestinal tumorigenesis in APC\textsuperscript{Min} background mice.\textsuperscript{61} A possible reason is that many important signaling pathways are downregulated in colorectal cancer, and loss of MBD2 leads to reexpression of these genes.\textsuperscript{62} Meanwhile, inhibition of MBD2 shows promising effects on suppression of the tumorigenesis of human lung cancer and colon cancer.\textsuperscript{63} Although MBD3 does not directly bind to methylated DNA, it regulates the methylation process via interactions with other proteins, such as MBD2 and HDAC. For example, application of an HDAC inhibitor in lung cancer cells upregulated p21 (also known as CDKN1A) and downregulated ErbB2, leading to inhibition of cancer cell growth. Silencing of MBD3 blocked the effects of an HDAC inhibitor.\textsuperscript{64} MBD3 and MBD2 form a complex, nucleosome remodeling and deacetylase (NuRD), which interacts with histone-demethylating enzymes to regulate gene expression in cancer.\textsuperscript{65} Mutation of MBD4 has been found in colorectal cancer, endometrial carcinoma and pancreatic cancer.\textsuperscript{66} Furthermore, this mutation unexpectedly affects the stability of the whole genome, not only CpG sites.\textsuperscript{67} Knockout of MBD4 indeed increased tumorigenesis in APC\textsuperscript{Min}-background mice, which makes MBD4 a tumor suppressor.\textsuperscript{68} MBD4 is important in DNA damage repair, given the interaction between MBD4 and MMR.\textsuperscript{69} In contrast, the expression of MeCP2 and the UHRF family tends to promote tumor growth.\textsuperscript{70,71} In the KAISO family, KAISO directly binds to p120\textsuperscript{cm}, a protein with an alternative location in some cancer cells, and they together regulate cell adhesion and motility.\textsuperscript{72,73} However, deficiency of ZBTB4 contributes to tumorigenesis (Table 1).  

DNA-demethylating enzymes  

DNA methylation is a stable and highly conserved epigenetic modification of DNA in many organisms.\textsuperscript{74} However, loss of 5-mC and DNA demethylation have been identified in different biologic processes. For example, DNA demethylation is important for primordial germ cells (PGCs) to gain pluripotent ability.\textsuperscript{75,76} In mammals, DNA demethylation is actively regulated by the TET protein family (ten-eleven translocation enzymes, TET1-3) via the removal of a methyl group from 5-mC. These three proteins differ from each other in terms of expression depending on the developmental stage and cell type.\textsuperscript{18} TETs oxidize 5-mC in an iterative manner and catalyze the conversion of 5-mC to 5-hydroxymethylcytosine (5-hmc), which is a key intermediate in the demethylation process.\textsuperscript{81} 5-hmc, as a relatively stable intermediate substrate, is less prone to further oxidation by TET proteins than 5-mC.\textsuperscript{82} However, over-expression of only TET1 and TET2 can cause a global decrease of 5-mC.\textsuperscript{18} Stepwise oxidation of 5-hmc by TET proteins can yield two products: 5-formylcytosine (5-fC) and 5-carboxylcytosine (5-caC).\textsuperscript{83} These two molecules can be excised by thymine-DNA glycosylase (TDG) and eventually be repaired to unmodified C. DNA demethylation or restoration of the unmodified cytosine can also occur passively through replication-dependent dilution of 5-mC.\textsuperscript{84}  

Disruption of normal DNA demethylation is thought to be associated with oncogenesis. TET proteins were initially associated with leukemia. Researchers have found that in a small number of AML patients, TET1 is fused to MLL via the chromosome translocation t(10;11)(q22;q23).\textsuperscript{85} Further studies found that TET2 was more widely expressed in different tissues than TET1 and TET3. Analyses revealed that mutation or deficiency of TET2 occurred in ~15% of patients with myeloid cancers, including myelodysplastic syndrome (MDS), myeloproliferative disorders, and AML.\textsuperscript{86} In patients with CML, mutation of TET2 has been detected in ~50% of patients.\textsuperscript{87} Although TET2 mutations have been found in several myeloid malignancies, their prognostic effect remains controversial. Based on the phenomenon that mutation of TET2 was elevated in patients whose disease transformed from chronic myeloid malignancy to AML, researchers considered that TET2 loss was important for cells to regain the ability to self-renew.\textsuperscript{88} The role of TET proteins has also been investigated in several solid tumors. Compared with surrounding normal tissues, 5-hmC is significantly reduced in human breast, liver, lung, pancreatic, and prostate cancers with reduced expression of TET family proteins.\textsuperscript{89} Deficiency of TET1 in prostate and breast cancer is associated with tumor cell invasion and breast xenograft tumor formation via the inhibition of the methylation of metalloproteinase (TIMP) family proteins 2 and...
Biology; otherwise, alterations in PTMs may be associated with key cellular events. In addition, lysine acetylation found outside histones, such as TFIIB, MCM3AP, ESCO, and ARD1. Knockout of CBP/p300 is lethal for early embryonic mouse models. The acetyl group transfer strategies for each HAT subfamily are different. For the GCN5 and PCAF family, the protein crystal structure shows a conserved glutamate in the active site. Blockade of this amino leads to a significantly decreased acetylation function. Similarly, there is also a conserved glutamate plus a cysteine residue located at active sites of MYST family proteins. Unlike the other two families, the p300/CBP HAT subfamily has two other potential conserved residues, a tyrosine and a tryptophan. Their catalytic mechanisms of acetyl group transfer can be divided into two groups. The GNAT family depends on a sequential ordered mechanism, whereas the members of the MYST family use a so-called ping-pong (i.e., double displacement) catalytic mechanism, which means that the acetyl groups are first transferred to a cysteine residue and then transferred to a lysine residue. In addition to differences in the acetyl transfer mechanism, HAT subfamilies, even different proteins in the same family, also have remarkable diversity in targeting sites. Appropriate acetylation within cells is important since upregulation or downregulation of HATs is associated with tumorigenesis or poor prognosis. Compared with solid tumors, the association between histone modifications and cancer has been widely investigated in hematological malignancies. Germline mutation of CBP results in Rubinstein-Taybi syndrome along with an increased predisposition to childhood malignancies. Meanwhile, loss of another family member, p300, has also been associated with hematological malignancies. Therefore, both CBP and p300 seem to function as tumor suppressors. During cancer development, the expression of HAT genes can be disrupted by chromosomal translocations, although these are rare events. Generation of the fused protein CBP-MOZ is the result of the (t(8,16)(p11,p13) translocation in AML. Translocation of t (10;16)(q22;p13) leads to the CBP-MORF chimera. Similarly, p300-MOZ, MLL-CBP, and MLL-p300 (MLL, mixed lineage leukemia) have also been identified in hematological malignancies. Generally, chromosomal rearrangements involving CBP are more common than those involving p300. Researchers have also investigated solid tumors, which are less mutated. The expression of translocated P300 in laryngeal squamous cell carcinoma (LSCC) tissue is much higher than that in adjacent normal tissue and is associated with advanced stage and poor prognosis. Missense point mutations in p300 are found in colorectal adenocarcinoma, gastric adenocarcinoma and breast cancer with quite low incidences. Rare inactivating mutations in CBP and PCAF have only been identified in cancer cell lines but not primary tumors. Based on these findings, we hypothesize that the differences between cell lines and primary tumors cannot be ignored. Amplified in breast cancer 1 (AIB1), also frequently called NCOA1, is overexpressed in ~60% of human breast cancers, and increased levels of AIB1 are associated with tamoxifen resistance and decreased overall survival. Steroid receptor coactivator 1 (SRC1) is also associated with the chromosomal translocation t(2;2)(q35;p23), which results in PAX3–NCOA1 gene fusion in rhabdomyosarcoma without a consistent genetic abnormality during embryonic development (Table 2).
| Enzyme/Synonym | Role in cancer | Cancer type | Associated biological process (involved mechanism and molecules) |
|---------------|----------------|-------------|-----------------------------------------------------------------|
| **Histone acetylases: the writers** |
| HAT1 / HAT1 | Promoter | Pancreatic cancer, nasopharyngeal cancer, hepatocellular carcinoma, esophageal carcinoma<sup>227–230</sup> | Promote cell apoptosis, proliferation, differentiation and cisplatin resistance, associated with poor prognosis and upregulates PD-L1 |
|             | Suppressor | Lung cancer, osteosarcoma<sup>231,232</sup> | Restores Fas expression and induces cancer cell apoptosis (Ras-ERK1/2 signaling) |
| GANT GCN5L2 / GCN5 | Promoter | Prostate cancer, breast cancer, non-small-cell lung cancer, colorectal cancer<sup>233–235</sup> | Promotes cell proliferation, apoptosis, EMT, poor prognosis of patients, promotion of E2F1, cyclin D1, and cyclin E1 expression (PI3K/PTEN/Akt signaling, TGF-β/Smad signaling pathway) |
| PCAF / Suppressor | Colorectal cancer, gastric cancer, prostate cancer, breast cancer<sup>236–238</sup> | Decreased PCAF is associated with 5-FU resistance, poor clinical outcome (PCAF-p16-CDK4 axis, p53, miR-17) |
| MYST1 HTATIP TIP60 | Promoter | Liver cancer, prostate cancer<sup>239,240</sup> | Promotes cancer cell EMT, metastasis, radioresistance |
| MYST2 MOF | Promoter | Prostate cancer<sup>241</sup> | Is associated with cell viability and invasion, and low Tip60 expression is correlated with poor overall survival and relapse-free survival |
| MYST3 MOZ | Promoter | Ovarian cancer, liver cancer, colorectal cancer, bladder cancer<sup>242–244</sup> | Promotes cell proliferation, enrichment of cancer stem-like cells, gemcitabine resistance (Wnt/β-catenin signaling) |
| MYST4 MORF | Promoter | Leukemia<sup>251</sup> | MORF-CREBBP fusion |
| P300 EP300, KAT3B | Promoter | Laryngeal squamous cell carcinoma, leukemia, nasopharyngeal carcinoma, hepatocellular carcinoma, cutaneous squamous cell carcinoma, head and neck squamous cell carcinoma, colorectal cancer, breast cancer, lung cancer, gastric cancer, prostate cancer, cervical cancer, pancreatic cancer<sup>246–247</sup> | Promotes cell proliferation, migration, invasion, EMT, and malignant transformation, is associated with advanced clinical stage, poor recurrence-free survival and overall survival, enhances ERα expression and contributes to tamoxifen resistance, castration resistance, and gemcitabine sensitivity, (p21, p27, β-catenin, MLL-p300, MOZ-p300 fusion, Smad2 and Smad3 in the TGF-β signaling pathway, p300/YY1/miR-500a-5p/HDAC2 signaling axis) |
| CBP CREBBP, KAT3A | Promoter | Lung cancer, leukemia, gastric cancer, ovarian cancer, prostate cancer, hepatocellular carcinoma<sup>248–254</sup> | Downregulation of P300 is associated with chemosensitivity to 5-FU treatment and doxorubicin resistance |
| SRC/p160 | Promoter | Prostate cancer, colon cancer, breast cancer, hepatocellular carcinoma, head and neck squamous cell carcinoma<sup>255–261</sup> | Is associated with drug resistance, a highly tumorigenic, cancer stem-like phenotype and enhances the activity of estrogen receptor-beta (ER-β) (CXCL8, PI3K/Akt/β-catenin/CBP axis); KAT6A-CREBBP, MOZ-CBP, MORF-CREBBP, MLL-CBP fusions in leukemia |
| NCOA1 SRC1 | Promoter | Lung cancer, prostate cancer<sup>262,263</sup> | Loss of CBP reduces transcription of cellular adhesion genes while driving tumorigenesis |
| NCOA2 TIF2 | Promoter | Prostate cancer, leukemia<sup>264,265</sup> | Promotes cell invasion, proliferation, metastasis, is associated with shorter overall survival and progression-free survival (M-CSF1, miR-4443, miR-105-1) |
| NCOA3 AIB1, ACTR | Promoter | Ovarian cancer, breast cancer, bladder cancer, gastric cancer, lung cancer, prostate cancer, hepatocellular carcinoma, esophageal squamous cell carcinoma, colorectal cancer, pancreatic cancer<sup>266–270</sup> | TIF2 is able to impair protumorigenic phenotypes |
| SRC/p160 | Promoter | Prostate cancer, colon cancer, breast cancer, hepatocellular carcinoma, head and neck squamous cell carcinoma<sup>264–267</sup> | Promotes cell proliferation, apoptosis, EMT, poor prognosis of patients, promotion of E2F1, cyclin D1, and cyclin E1 expression (PI3K/PTEN/Akt signaling, TGF-β/Smad signaling pathway) |
| NCOA1 SRC1 | Promoter | Lung cancer, leukemia<sup>268–269</sup> | Is associated with resistance to AR antagonism and bicalutamide; MOZ-TIF2 fusion in leukemia |
| NCOA2 TIF2 | Promoter | Colorectal cancer, liver cancer<sup>270,271</sup> | TIF2 is able to impair protumorigenic phenotypes |
| NCOA3 AIB1, ACTR | Promoter | Ovarian cancer, breast cancer, bladder cancer, gastric cancer, lung cancer, prostate cancer, hepatocellular carcinoma, esophageal squamous cell carcinoma, colorectal cancer, pancreatic cancer<sup>272–275</sup> | Promotes cell proliferation, EMT, metastasis, invasiveness and is correlated to higher estrogen receptor expression, poor PFS and OS and predicts resistance to chemoradiotherapy (AKT, E2F1, SNAIL1, cyclin E, cdk2, p53, matrix metalloproteinase 2 (MMP2) and MMP9 expression); however, high AIB1 expression has been correlated to both a good response to adjuvant tamoxifen and tamoxifen resistance. |
| Enzyme | Synonym | Role in cancer | Cancer type | Associated biological process (involved mechanism and molecules) |
|--------|---------|----------------|-------------|---------------------------------------------------------------|
| ATF-2  | CREB2, CREBP1 | Promoter | Pancreatic cancer, lung cancer, renal cell carcinoma, leukemia<sup>276-278</sup> | Promotes cell proliferation, EMT, gemcitabine sensitivity (JNK/c-Jun and p38 MAPK/ATF-2 pathways, mIR-451); however, the level of ATF-2 is a key determinant of the sensitivity to tamoxifen |
| TFIIC  | / | Promoter | Ovarian cancer<sup>279</sup> | TFIIC is overexpressed in cancer tissues |
| TAF1   | TAFI250 | / | / | / |
| CLOCK  | KIAA0334 | Promoter | Ovarian cancer, breast cancer<sup>280,281</sup> | Promotes cell proliferation, migration, and invasion, is associated with drug resistance (cisplatin) |
| CIITA  | MHC2TA | Suppressor | Breast cancer, colorectal cancer, gastric cancer, head and neck cancer, hepatocellular carcinoma<sup>283-285</sup> | Is associated with cancer progression and metastasis |
| MGEAS  | NCOAT | Promoter | Laryngeal cancer<sup>286</sup> | MGEAS transcript levels were significantly lower in grade II and III than in grade I tumors; associated with lymph node metastasis |
| CDY    | / | / | / | / |
| Acetyl-lysine binding protein: the readers | BRD and extraterminal domain (BET) proteins family | Breast cancer, prostate cancer, gastric tumors, lung cancer, ovarian carcinoma, pancreatic cancer, hematologic malignancy, Ewing sarcoma, glioblastoma, melanoma<sup>288-291</sup> | Is associated with cell proliferation, self-renewal, metabolism, metastasis, and expression of immune checkpoint molecules (oncogenic AR and MYC signaling, AMIGO2-PTK7 axis, Jagged1/Notch1 signaling, IKK activity) |
| Histone deacetylases (HDACs): the erasers | HDAC Class I | Thyroid cancer, lung cancer, ovarian cancer, breast cancer, colorectal cancer, prostate cancer, gastro cancer<sup>292-295</sup> | Promotes cell invasion, viability, apoptosis, EMT; is associated with chemotherapy response. (CXCL8, P53, p38 MAPK, miRNA-34a) |
| HDAC1  | / | Promoter | Pancreatic cancer, colon cancer, lung cancer, squamous cell carcinoma, breast cancer, prostate cancer, gastric cancer, ovarian cancer, lung cancer<sup>296-300</sup> | Promotes cell proliferation, metastasis, invasion, clonal expansion and BET (E-cadherin, p63, mTORC1, AKT, PELP1/HDAC2/miR-200, p300/Y1/miR-500a-5p/HDAC2 axis, Sp1/HDAC2/p27 axis) |
| HDAC2  | / | Promoter | Colorectal cancer, pancreatic cancer, breast cancer, colorectal cancer, prostate cancer, esophageal cancer, lung cancer<sup>291-304</sup> | Promotes cell proliferation and invasion, migration, chemosensitivity; increases PD-L1 expression (NF-κB signaling) |
| HDAC3  | / | Promoter | Cervical cancer, breast cancer, colon cancer<sup>305-307</sup> | Promotes cell migration, affects cell morphology and promotes the cell cycle (p53, HDAC8/YY1 axis) |
| HDAC8  | / | Promoter | Breast cancer<sup>308</sup> | HDAC8 suppresses EMT (HDAC8/FOXA1 signaling) |
| HDAC4  | / | Promoter | Head and neck cancer, breast cancer, colorectal cancer, gastric cancer, ovarian cancer, prostate cancer<sup>309-311</sup> | Promotes cell viability, drug resensitization (tamoxifen, platinum) (STAT1, p21, mIR-10b) |
| HDAC5  | / | Promoter | Breast cancer, colorectal cancer, lung cancer, prostate cancer<sup>312,313</sup> | Promotes cell proliferation, invasion, migration and EMT; is associated with hormone therapy resistance (HDAC5-LSD1 axis, Survivin and mIR-125a-5p, mIR-589-5p) |
| HDAC6  | / | Promoter | Cervical cancer, breast cancer, colorectal cancer, gastric cancer, lung cancer, prostate cancer, liver cancer, ovarian cancer<sup>314-317</sup> | Promotes pluripotency of CSCs, cancer cell proliferation and migration (α-tubulin, heat shock protein (HSP) 90, the NF-κB/MMP2 pathway, JNK/c-Jun pathway, miR-22, miR-221) |
| HDAC7  | / | Promoter | Breast cancer, colorectal cancer, prostate cancer, ovarian cancer<sup>318-320</sup> | Is associated with cancer stem cell-specific functions, tumor growth and invasion, and therapy resistance (mIR-489, mIR-34a) |
| HDAC9  | / | Promoter | Breast cancer<sup>321</sup> | Enhances invasive and angiogenic potential (mIR-206) |
| HDAC9  | / | Suppressor | Lung cancer<sup>322</sup> | HDAC9 is downregulated in adenocarcinomas; is associated with tumor growth ability |
| Enzyme          | Synonym | Role in cancer | Cancer type                              | Associated biological process (involved mechanism and molecules)                                                                 |
|---------------|---------|---------------|------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| HDAC10        | /       | Promoter      | Ovarian cancer, lung cancer\(^{323,324}\) | Promotes cell proliferation, reduced DNA repair capacity and sensitization to platinum therapy (AKT phosphorylation)          |
| HDAC Class III: sir2-like proteins (sirtuins) |         |               |                                          |                                                                                                                               |
| Sirt1         | /       | Promoter      | Breast cancer, colorectal cancer, prostate cancer, liver cancer, lung cancer, pancreatic cancer, cervical cancer, gastric cancer, ovarian cancer\(^{325-327}\) | Promotes cell proliferation, migration, metastasis, EMT, metabolic flexibility and self-renewal of cancer stem cells, chemoresistance (miR-30a, miR-15b-5p) |
|               |         |               |                                          | Highly expressed in stem-like cells and promotes migration, invasion and metastasis (p53, RA/ERK/JNK/MMP-9 pathway)               |
|               |         | Suppressor    | Breast cancer, prostate cancer lung cancer\(^{333-333}\) | Sensitizes cancer cells to intracellular DNA damage and the cell death induced by oxidative stress, and low Sirt2 levels were associated with poor patient survival (p27) |
| Sirt3         | /       | Promoter      | Cervical cancer, lung cancer\(^{334,335}\) | Is associated with PD-L1-induced lymph node metastasis (p53)                                                                      |
|               |         | Suppressor    | Pancreatic cancer, breast cancer, prostate cancer, gastric cancer, ovarian cancer\(^{329-330}\) | Loss of SIRT3 leads to reactive oxygen species (ROS) generation that amplifies HIF-\(\alpha\) stabilization; metastasis (c-MYC, CagA, PI3K/Akt pathway, Wnt/\(\beta\)-catenin pathway, AMP-activated protein kinase (AMPK) |
| Sirt4         | /       | Suppressor    | Pancreatic cancer, thyroid cancer, gastric cancer, colorectal cancer\(^{336,340}\) | Promotes cell proliferation, aerobic glycolysis, migration and invasion, and inhibition of glutamine metabolism (E-cadherin) |
| Sirt5         | /       | Promoter      | Colorectal cancer, lung cancer, breast cancer\(^{341-343}\) | Promotes autophagy, cell proliferation, and drug resistance, and is associated with poor clinical outcomes |
| Sirt6         | /       | Promoter      | Pancreatic cancer, lung cancer, prostate cancer\(^{346-348}\) | Enhances cytokine production, and promotes EMT, cell migration and tumor metastasis, and predicts poor prognosis (ERK1/2/MPP9 pathway, SIRT6/Snail/ KLIF4 axis) |
|               |         | Suppressor    | Pancreatic cancer, breast cancer, liver cancer\(^{349,350}\) | Promotes increased glycolysis, cancer cell proliferation and tumor growth, and is associated with paclitaxel, eripubicin, and trastuzumub sensitivity (survivin, NF-\(\kappa\)-B pathway) |
| Sirt7         | /       | Promoter      | Colorectal cancer, gastric cancer, bladder cancer\(^{351,352}\) | Accelerates cell growth, proliferation, motility and apoptosis (MAPK pathway)                                                   |
|               |         | Suppressor    | Pancreatic cancer, breast cancer, lung cancer, colorectal cancer\(^{353-355}\) | Sensitizes to gemcitabine and radiotherapy, and low levels of SIRT7 are associated with an aggressive tumor phenotype and poor outcome (TGF-\(\beta\) signaling, p38 MAPK) |
| HDAC Class IV |         |               |                                          |                                                                                                                               |
| HDAC11        | /       | Promoter      | Liver cancer, Hodgkin lymphoma, neuroblastoma, colorectal cancer, prostate cancer, breast cancer, ovarian cancer\(^{356-359}\) | Promotes the mitotic cell cycle, cell apoptosis, is associated with cancer progression and survival (OX40 ligand, p53)            |

|\(EMT\) epithelial-mesenchymal transition, \(PI3K\) phosphatidylinositol 3-kinase, \(TGF-\beta\) transforming growth factor \(\beta\), \(ER\) estrogen receptor, \(CSF\) colony-stimulating factor, \(AR\) androgen receptor, \(MMP\) matrix metalloproteinase |
as the first and sole histone-binding module that contains a hydrophobic pocket to identify acetyl-lysine. The specificity of different BRDs depends on the sequences within the loops that form the hydrophobic pocket. Therefore, each BRD has a preference for different histones. In addition to their recognition of acetyl-lysine, BRDs are also capable of interacting with other chromatin molecules, such as plant homeodomain (PHD) finger motifs or another BRD. To date, 42 proteins containing bromodomains and 61 unique bromodomains have been discovered. Different BRD-containing proteins contain one to six BRDs. Intriguing, the most notable and well-studied bromodomain proteins are also HATs, such as PCAF, GCNS, and p300/CBP. Yaf9, ENL, AF9, Tau14, Sas5 (YEATS), and double PHD finger (DPF) have also been discovered to be acetyl-lysine reader domains. Human MOZ and DPF2 are two proteins containing the DPF domain. Mutations in the YEATS and DPF domains are associated with cancer. For example, mutation of AF9 has been found in hematological malignancies, and ENL dysregulation leads to kidney cancer.

Another important family is the BRD and extraterminal domain (BET) protein family, including BRD2, BRD3, BRD4, and BRD7, and this family shares two conserved N-terminal bromodomains and a more divergent C-terminal recruitment domain. These bromodomain proteins are critical as mediators of gene transcriptional activity. Of note, bromodomains have also been found in some histone lysine methyltransferases, such as ASH1L and MLL. BRDs are expressed not only in the nucleus but also in the cytoplasm, and are also capable of mono-ADP-ribosyltransferase and HDAC activities. Notably, HDACs are also capable of regulating gene transcription by deacetylating other proteins that are responsible for epigenetic events, such as DNMTs, HATs, and HDACs. Another phenomenon is that some HDACs have to form a complex along with other components to function as transcriptional corepressors, which provides ideas and methods to design novel HDAC inhibitors. The Sin3, NuRD, and CoREST complexes are three complexes containing HDAC1 and HDAC2. Studies have found that purified HDAC1 or HDAC2 without associated components shows fairly weak deacetylation activity in vitro. HDAC3 interacts with the corepressors SMRT/NCoR to form the functional complexes, which significantly increases HDAC3 activity. NCoR also interacts with HDAC1, HDAC2 and the class II deacetylases HDAC4, HDAC5, and HDAC7, but usually not in the form of a complex. Deleted in breast cancer 1 (DBC1) and active regulator of SIRT1 (AROS) are two proteins that are able to bind to SIRT1, whereas their interactions present opposite functions. The DBC1/SIRT1 complex inhibits the deacetylation activity of SIRT1, whereas the combination of AROS and SIRT1 stimulates the activity of SIRT1.

Histone deacetylases. Histone deacetylases (HDACs) have recently attracted increasing attention. In humans, the genome encodes 18 HDACs. In contrast to the function of HATs, HDACs usually act as gene silencing mediators and repress transcription. Similarly, HDACs are expressed not only in the nucleus but also in the cytoplasm, and their substrates are also limited to histones. Based on sequence similarity, HDACs can be divided into four classes: class I HDACs, yeast Rpd3-like proteins, are transcriptional corepressors and have a single deacetylase domain at the N-terminus and diversified C-terminal regions; class II HDACs, yeast Hda1-like proteins, have a deacetylase domain at a C-terminal position; class III HDACs, yeast silent information regulator 2 (Sir2)-like proteins (SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7); and class IV involves one protein (HDAC11). The class IV protein shares sequence similarity with both class I and II proteins. Classes I, II, and IV are included in the histone deacetylase family, whereas class III HDACs belong to the Sir2 regulator family. The catalytic mechanisms for these two families are different; classes I, II, and IV are Zn\(^{2+}\)-dependent HDACs, whereas Sir2-like proteins (sirtuins) are nicotinamide adenine dinucleotide (NAD\(^{+}\))-dependent HDACs and are also capable of mono-ADP-ribosyltransferase activity, another pattern of histone modification. Intriguingly, SIRT4 is thought to have more mono-ADP-ribosyltransferase activity than HDAC activity. SIRT2 and SIRT6 seem to have equal levels of both mono-ADP-ribosyltransferase and HDAC activities. Moreover, after revealing the crystal structure of SIRT5, researchers found that SIRT5 is also a lysine desuccinylase and demalonylase. Therefore, the diversity of the sirtuin family makes them a group of multifunctional enzymes.

So far, the major known recognition sites of each HDAC are different, and these largely remain to be uncovered. For example, HDAC3 is thought to deacetylate H4K8 and H4K12, but in an HDAC3-knockout HeLa cell line, the acetylation levels of H4K8 and H4K12, even the overall acetylation levels of H3 and H4, were comparable with those in wild-type cells. Nevertheless, HDAC1 or HDAC3 siRNA can indeed increase the acetylation levels of H3K9 and H3K18. Therefore, partially because of the functional complementation and diversity within HDAC families, especially in class I, II, and IV, it is difficult to identify the specific substrates of certain HDACs. However, the substrates of the sirtuin family are quite clear. It is notable that because SIRT4 and SIRT5 are only located in mitochondria, they have no effect on histones. However, nonhistone lysine acetylation is also prevalent, since more than 3600 acetylation sites on 1750 proteins have been identified. The tumor suppressor p53 and the cytoskeletal protein α-tubulin are two representative substrates of HDACs. Notably, HDACs are also capable of regulating gene transcription by deacetylating other proteins that are responsible for epigenetic events, such as DNMTs, HATs, and HDACs. Another phenomenon is that some HDACs have to form a complex along with other components to function as transcriptional corepressors, which provides ideas and methods to design novel HDAC inhibitors. The Sin3, NuRD, and CoREST complexes are three complexes containing HDAC1 and HDAC2. Studies have found that purified HDAC1 or HDAC2 without associated components shows fairly weak deacetylation activity in vitro. HDAC3 interacts with the corepressors SMRT/NCoR to form the functional complexes, which significantly increases HDAC3 activity. NCoR also interacts with HDAC1, HDAC2 and the class II deacetylases HDAC4, HDAC5, and HDAC7, but usually not in the form of a complex. Deleted in breast cancer 1 (DBC1) and active regulator of SIRT1 (AROS) are two proteins that are able to bind to SIRT1, whereas their interactions present opposite functions. The DBC1/SIRT1 complex inhibits the deacetylation activity of SIRT1, whereas the combination of AROS and SIRT1 stimulates the activity of SIRT1.

Histone acetylation "readers", bromodomain proteins play important roles in tumorigenesis. BRD4 recruits the positive transcription elongation factor complex (P-TEFb), a validated target in chronic lymphocytic leukemia associated with transcription elongation factor complex (P-TEFb), a validated protein (HDAC11). The class IV protein shares sequence similarity to SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7; and class IV involves one C-terminal region (HDAC11), and double PHD finger (DPF) have also been discovered to be acetyl-lysine reader domains. In this review, we focus on the role of BRDs in tumorigenesis. As histone acetylation "readers", bromodomain proteins play important roles in tumorigenesis. BRD4 recruits the positive transcription elongation factor complex (P-TEFb), a validated target in chronic lymphocytic leukemia associated with c-Myc activity. Chromosomal translocation of BRD4, via the t(15;19) translocation, results in the generation of the fusion protein BRD4-NUT (nuclear protein in testis), which is found in NUT midline carcinoma (NMC). Importantly, inhibition of BRD4-NUT induces differentiation of NMC cells. Moreover, BRD4 is required for the maintenance of AML with sustained expression of Myc (Table 2).
dimethylated, whereas lysine is also capable of being trimethylated. Histone methylation can either promote or inhibit gene expression, which depends on the specific situation. For example, lysine methylation at H3K9, H3K27, and H4K20 is generally associated with suppression of gene expression, whereas methylation of H3K4, H3K36, and H3K79 induces gene expression. Mutation of H3K27M (lysine 27 to methionine) and H3K36M are two important oncogenic events, and H3K27M and H3K36M serve as drivers of pediatric gliomas and sarcomas. H3K27M has been identified in more than 70% of diffuse intrinsic pontine gliomas (DIPGs) and 20% of pediatric glioblastomas, which results in a global reduction in the trimethylation of H3K27 (H3K27me3). However, the H3K36M mutation impairs the differentiation of mesenchymal progenitor cells and generates undifferentiated sarcoma, leading to increased levels of H3K27me3 and global loss of H3K36 (me2 and me). Meanwhile, depletion of H3K36 methyltransferases results in similar phenotypes to those seen with H3K36M mutation. To date, KMTs (lysine methyltransferases) have been better studied than arginine methyltransferases (PRMTs) due to their sequence of discovery, different prevalence and impact. Their targets are not limited to only histones, they also modify other key proteins, such as the tumor suppressor p53, TAF10, and Piwi proteins.

Histone methyltransferases. All KMTs contain a 130-amino-acid conserved domain, the SET (suppressor of variegation, enhancer of Zeste, trithorax) domain, except for DOT1L. The SET domain is responsible for the enzymatic activity of SET-containing KMTs. Instead of methyating lysine residues in histone tails, DOT1L methylates lysine in the globular core of the histone, and its catalytic domain is more similar to that of PRMTs. The enzymatic activity of KMTs results in the transfer of a methyl group from S-adenosylmethionine (SAM) to the ε-amino group of a lysine residue. The first identified KMT was SUV39H1, which targets H3K9. Sequentially, more than 50 SET-containing proteins have been identified with proven or predicted lysine methylation potential. Of note, KMTs are highly specific enzymes, meaning that they are highly selective for lysine residues they can methylate and the specific methylation degree they can achieve. For example, SUV39H1 and SUV39H2 specifically methylate histone 3 at lysine 9 (H3K9), and DOT1L only methylates H3K79. Based on their structure and sequence around the SET domain, generally, KMTs can be divided into six groups, SUV39, SET1, SET2, EZH, SMYD, and RIZ (PRDM) (reviewed by Volkel and Angard). The Pre-SET domain of the SUV39 family contains nine conserved cysteines that coordinate with three zinc ions to function. The SET1 family members share a similar Post-SET motif that contains three conserved cysteine residues. The SET2 family possesses an AWS motif that contains 7–9 cysteines. Their SET domain is located between the AWS motif and a Post-SET motif. The members of the enhancer of zeste homolog (EZH) family are the catalytic components of polycomb repressive complexes (PRCs), which are responsible for gene silencing. EZH proteins have no Post-SET motif but have 15 cysteines in front of the SET domain and show no methylated activity as isolated proteins. PRC2 shows lysine methylation activity through its catalytic components, EZH2 or its homolog EZH1. EZH2 can methylate not only histone H3 but also histone H1 at lysine 26. The SMYD family members, which are SET and MYND domain-containing proteins, possess a MYND (myeloid-nervy-DEAF1) domain, a zinc-finger motif responsible for protein–protein interaction. The RIZ (PRDM) family is a large family containing a homolog of the SET domain, the PR domain. The PR and SET domains share 20–30% sequence identity and are both capable of inducing histone H3 methylation. However, most members of the RIZ family responsible for histone methylation are still unknown. So far, two of them have been proven to induce the methylation of histones: PRDM2 (RIZ1) is associated with H3K9 methylation; and Meisetz, the mouse homolog of PRDM9, trimethylates H3K4. Meanwhile, PRDM1 has been identified to interact with EHMT2, a member of the SUV39 family. PRDM6 acts as a transcription suppressor by interacting with class I HDACs and EHMT2 to induce cell proliferation and inhibit cell differentiation. Meanwhile, the recruitment of EHMT2 is based on the formation of a complex with PRDM1. Due to the lack of a characteristic sequence or structure flanking the SET domain, other SET-containing KMTs, such as SET7/9, SET8, SUV4-20H1, and SUV4-20H2, cannot be classified into these families. Notably, some KMTs contain more than one domain, which allows them to interact with other proteins, especially other epigenetic modifying proteins. SUV39H1 possesses a chromodomain that directly binds to nucleic acids and forms heterochromatin. MLL1 recognizes unmethylated DNA through its Cpg-interacting CXXC domain. SETDB1 contains an MBD that interacts with methylated DNA. The Tudor domain in SETDB1 may potentially recognize the methylation of lysine residues. ASH1 is able to interact with CBP, a HAT, via a bromodomain within ADH1.

Protein arginine methyltransferases (PRMTs) can be divided into two groups. Among the nine PRMTs, only PRMT5, PRMT7, and PRMT9 are type II PRMTs, and the other five PRMTs, except for PRMT2, are type I PRMTs. PRMT2 was identified by sequence homology but has not shown any catalytic activity during investigations, although PRMT2 acts as a strong coactivator for androgen receptor (AR), which is thought to be associated with arginine methylation. Both types of PRMTs first catalyze the formation of monomethylarginine as an intermediate. However, sequentially, type I PRMTs can form asymmetric dimethylarginine (ADMA, Rme2a), but type II PRMTs form symmetric dimethylarginine (SDMA, Rme2s). Rme2a means two methyl groups on one ω-amino group, whereas an Rme2s has one methyl group on each ω-amino group. PRMT1–PRMT8 were investigated by Herrmann and Fackelmayer, and FBXO11 was identified as PRMT9, which symmetrically dimethylates arginine residues.

Most enzymes for histone methylation are substrate-specific proteins; therefore, alterations in the aberrant expression of enzymes are usually associated with specific histone residue mutations. One of the best-known examples of alterations in tumorigenesis is H3K4me3, which is associated with biphenotypic (mixed lineage) leukemia (MLL). The location of the MLL gene is where chromosomal translocations in AML and ALL usually occur. When the MLL gene is translocated, the catalytic SET domain is lost, and most proteins in MLL translocations include fusion proteins, which recruit DOT1L. Maintenance of MLL-associated ALL depends on the methylation of H3K79 catalyzed by DOT1L. Therefore, DOT1L is usually associated with hematological malignancies rather than solid tumors. Alteration of the EZH2-induced methylation of H3K27 has been observed in multiple cancers, including various solid tumors (prostate, breast, kidney, bladder, and lung cancers) and hematological malignancies. Meanwhile, overexpression of EZH2 has been found in multiple cancers and is associated with poor prognosis. Different mechanisms have been proposed to describe the role of EZH2 in tumorigenesis (Table 3).

Methyl-histone recognition proteins. “Readers” of histone methylation contain several specific domains recognizing lysine or arginine methylation, such as a chromodomian, the WD40 repeat, the MBT (malignant brain tumor) domain, the Tudor domain and the PHD (plant homeodomain) finger motif. Representative chromodomian-containing proteins in humans are HP1 and Chd1, which can recognize H3K9me and H3K27me, respectively. WDR5 is a protein containing WD40 repeats. In addition to H3K4me, WDR5 prefers to bind to H3K4me2 via a histone-methylating complex and is required for maintaining H3K4me3. Later, WDR5 was shown to directly read H3R2, a “WIN” motif of MLL1, as well as symmetrical H3R2 dimethylation.

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| Enzymes  | Synonyms                  | Role in cancer                                                                 | Cancer type                                                                 | Mechanism                                                                                                                                                                           |
|---------|---------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| KMT1A   | SUV39H1, MG44, SUV39H     | Promoter                                                                        | Gastric cancer, prostate cancer, breast cancer, lung cancer, colorectal cancer, bladder cancer | Promotes cell migration and cancer stem cell self-renewal (KMT1A-GATA3-STAT3 axis)                                                                                              |
|         |                           |                                                                                  |                                                                            |                                                                                                                                                                                   |
| KMT1B   | FLJ23414, SUV39H2         | Promoter                                                                        | Breast cancer, cervical cancer                                              |                                                                                                                                                                                   |
| KMT1C   | EMT2, G9A, BATB, NG36    | Promoter                                                                        | Colorectal cancer, lung cancer, gastric cancer                              |                                                                                                                                                                                   |
| KMT1E   | SETDB1, ESET, KG1T       | Promoter                                                                        | Breast cancer, colorectal cancer, hepatozellary carcinoma, liver cancer      |                                                                                                                                                                                   |
| SET1    |                           |                                                                                  |                                                                            |                                                                                                                                                                                   |
| KMT2A   | ML1, HRX, TRX1, ALL-1    | Promoter                                                                        | Head and neck cancer, pancreatic cancer, prostate cancer                     |                                                                                                                                                                                   |
| KMT2B   | ALR, MLL2                | Promoter                                                                        | Bladder cancer, lung cancer, breast cancer                                  |                                                                                                                                                                                   |
| KMT2C   | MLL3, HALR               | Suppressor                                                                       | Colorectal cancer, esophageal squamous cell carcinoma                        |                                                                                                                                                                                   |
| KMT2E   | MLL4, HRX2               | Promoter                                                                        | Breast cancer                                                               |                                                                                                                                                                                   |
| KMT2F   | SET1A                    | Promoter                                                                        | Liver cancer                                                                |                                                                                                                                                                                   |
| EZH1    | KIAA0388                 | Promoter                                                                        | Breast cancer, prostate cancer, bladder cancer, colorectal cancer, liver cancer, gastric cancer, melanoma, lymphoma, myeloma, Ewing's sarcoma, glioblastoma, thyroid carcinoma, esophageal squamous cell cancer, lung cancer, ovarian cancer, | Promotes cell proliferation, colony formation, migration and tumor metastasis; is associated with cancer cell stem cell maintenance; predicts chemotherapeutic efficacy and response to tamoxifen therapy (E-cadherin, RUNX3, MEK-ERK1/2-Elk-1 pathway) |
| EZH2    | KMT6, ENX-1, MGCO9169    |                                                                                  |                                                                            |                                                                                                                                                                                   |
| SET2    |                           |                                                                                  |                                                                            | Maintains genome integrity and attenuates cisplatin resistance (ERK signaling pathway)                                                                                             |
| KMT3A   | SETD2, SET2, HIF-1,      | Suppressor                                                                       | Renal cancer, lung cancer                                                     |                                                                                                                                                                                   |
| WHSC1   | NSD2, WHS, TRX5          | Promoter                                                                        | Prostate cancer, gastric cancer                                              | Promotes cell invasive properties, EMT and cancer metastasis                                                                                                                                                                                    |
| WHSC1L1 | NSD3, MGC126766          | Promoter                                                                        | Breast cancer, head and neck cancer                                           | Is associated with BRx overexpression and enhances the oncogenic activity of EGFR                                                                                                 |
| RIZ (PRDM) |                   |                                                                                  |                                                                            |                                                                                                                                                                                   |
| PRDM1   | BLM1P                    | Promoter                                                                        | Pancreatic cancer, breast cancer                                              | Promotes cell invasiveness and cancer metastasis                                                                                                                                 |
| PRDM2   | RIZ                      | Promoter                                                                        | Colorectal cancer, breast cancer                                              |                                                                                                                                                                                   |
| PRDM3   | EV1, MDS1-EVII           | Promoter                                                                        | Ovarian cancer, nasopharyngeal carcinoma                                     |                                                                                                                                                                                   |
| PRDM4   | PFM1                     | Promoter                                                                        | Breast cancer                                                               |                                                                                                                                                                                   |
| PRDM5   | PFM2                     | Suppressor                                                                       | Colorectal cancer, gastric cancer, cervical cancer                           |                                                                                                                                                                                   |
| PRDM9   | PFM6                     | Promoter                                                                        | N/A                                                                        | Impairs genomic instability and drives tumorigenesis                                                                                                                                 |
| PRDM14  | PFM11                    | Promoter                                                                        | Testicular cancer, pancreatic cancer                                         |                                                                                                                                                                                   |
| PRDM16  | MEL1, PFM13              | promoter                                                                        | Gastric cancer                                                              |                                                                                                                                                                                   |

| Histone methyltransferases (lysine): the writers for lysine |
|----------------------------------------------------------------|
| SUV39H                                                          |
| KMT1A                                                         |
| KMT1B                                                         |
| KMT1C                                                         |
| KMT1E                                                         |
| SET1                                                          |
| KMT2A                                                         |
| KMT2B                                                         |
| KMT2C                                                         |
| KMT2D                                                         |
| KMT2E                                                         |
| KMT2F                                                         |
| EZH1                                                          |
| EZH2                                                          |
| SET2                                                          |
| KMT3A                                                         |
| WHSC1                                                         |
| WHSC1L1                                                       |
| RIZ (PRDM)                                                    |
| PRDM1                                                         |
| PRDM2                                                         |
| PRDM3                                                         |
| PRDM4                                                         |
| PRDM5                                                         |
| PRDM9                                                         |
| PRDM14                                                        |
| PRDM16                                                        |
| Enzymes | Synonyms | Role in cancer | Cancer type | Mechanism |
|---------|----------|----------------|-------------|-----------|
| SMYD    |          | Promoter       | Pancreatic cancer, gastric cancer, breast cancer, lung cancer | Promotes cancer cell proliferation and survival (STAT3, EML4-ALK, p63) |
| KMT3C   | SMYD2    | Promoter       | Liver and colon cancer, prostate cancer, breast cancer | Promotes cell proliferation, invasion, EMT and cancer stem cell maintenance (Myo, MMP-9, Ctnnb1, JAK/Stat3 pathway, Wnt pathway, androgen receptor transcription) |
| KMT3E   | SMYD3, ZMYND1, ZNFN3A1, FLJ21080 | Promoter       | Liver and colon cancer | Increases EMT, cancer stemness and tumorigenic potential and is required for MLL rearrangement |
| SMYD4   | ZMYND21  | Suppressor     | Breast cancer | SMYD4 acts as a suppressor in tumorigenesis |
| Others  |          |                |             |           |
| DOT1L   | KMT4     | Promoter       | MLL-rearranged leukemia, colorectal cancer, breast cancer, ovarian cancer | Promotes cell proliferation, migration, invasion, and EMT (MIR-502) |
| SET8    | KMT5A, SETD8, PR-set7 | Promoter       | Liver and colon cancer, prostate cancer, ovarian cancer, lung cancer | Promotes cell survival and colony formation and contributes to increased susceptibility to cancer |
| SUV4-20H2 | KMT5C, MGC2705 | Suppressor     | Breast cancer | Promotes cell proliferation, EMT and the generation of cancer stem cells; a low level of SET7/9 is correlated with clinical aggressiveness and worse prognosis (β-catenin stability) |
| SET7/9  | SETD7, KMT7 | Suppressor     | Breast cancer, gastric cancer, AML, lung cancer | SHARPIN-PRMT5-H3R2me1 axis |
|         |          |                |             |           |
| Histone methyltransferases (arginine): the writers for arginine |
| PRMT1   | ANM1, HCP1, IR1B4 | Promoter       | Breast cancer, colon cancer, gastric cancer, lung cancer | Promotes EMT, cancer cell migration, and invasion and is associated with chemosensitivity and poor clinical and histological parameters |
| PRMT2   |          | Suppressor     | Breast cancer | Inhibits cell proliferation and invasion in pancreatic cancer |
| PRMT4   | CARM1    | Promoter       | Ovarian cancer, breast cancer, liver cancer, colorectal cancer, prostate cancer | Induces cell cycle arrest and apoptosis in breast cancer |
| PRMT5   | JBP1, SKB1, IBP72 | Suppressor     | Breast cancer, prostate cancer, colorectal cancer, lung cancer | Promotes cell proliferation and blocks cell differentiation (Wnt/β-catenin signaling) |
| PRMT6   | HRMT1L6  | Suppressor     | Breast cancer | Inhibits glutamine metabolism and suppresses cancer progression |
| PRMT7   | FLJ10640, KIAA1933 | Suppressor     | Hepatocellular carcinoma | Promotes cell survival, proliferation, invasiveness and sensitivity to 5-Fluorouracil (5-FU) (SHARPIN-PRMT5-H3R2me1 axis) |
| PRMT8   | HRMT1L3, HRMT1L4 | Promoter       | Lung cancer, breast cancer | High PRMT5 expression favors a better prognosis in BC patients |
| PRMT9   | FBXO11   | Promoter       | Breast cancer | Is associated with cell apoptosis, invasiveness and viability (P3K/AKT/mTOR pathway, HSR2me2a axis) |
| PRMT10  |          | Overexpression of PRMT8 is correlated with decreased patient survival | Fuels tumor formation via restraint of the p53/p21 pathway |

**Methyl-histone recognition proteins: the readers**

| Chromodomain |
|--------------|
| HP1          | Promoter | Breast cancer | Overexpression of HP1 is associated with breast cancer progression |
| Chd1         | Promoter | Prostate cancer | Is associated with cell invasiveness, double-strand break repair and response to DNA-damaging therapy |
| WD-40 repeat domain |
| WD40         | /        | /              | Loss of MAP3K7 and CHD1 promotes an aggressive phenotype in prostate cancer |

| MBT domain |
|------------|
| BPTF        | Promoter | Lung cancer, hepatocellular carcinoma | Promotes cell proliferation, migration, stem cell-like traits and invasion (miR-3666) |
| L3MBTL1     | Suppressor | Breast cancer | Expression of L3MBTL1 is associated with a low risk of disease recurrence and breast cancer-related death |
| ING2        | Promoter | Colon cancer | Increases invasion by enhancing MMP13 expression |
|             | Suppressor | Lung cancer | Suppresses tumor progression via regulation of p53 |
| Enzymes | Synonyms | Role in cancer | Cancer type | Mechanism |
|---------|----------|----------------|-------------|-----------|
| **Tudor domains** | | | | |
| JMD2A | Promoter | Breast cancer, liver cancer, colon cancer | Breast cancer, liver cancer, pancreas cancer, gastric cancer | Promotes cells apoptosis and proliferation and contributes to tumor progression (AR/HR, miR372) Low JMD2A correlates with poor prognostic features and predicts significantly decreased overall survival |
| KDM1A | LSD1 | Promoter | Breast cancer, lung cancer, prostate cancer, liver cancer, pancreatic cancer | Contributes to cell proliferation and stem cell maintenance and self-renewal (p21, AR, HIF1α-dependent glycolytic process) Inhibits invasion and metastatic potential |
| KDM2A | JHDMA, CXXC8 | Promoter | Breast cancer, gastric cancer, lung cancer, cervical cancer | Promotes cell proliferation, metastasis, and invasiveness (HDAC3, TET2) Promotes cancer cell proliferation and metastasis (c-Myc, Wnt/β-catenin signaling, glycolysis, HIF1α) |
| KDM3A | JHDMA2, JMD1A | Promoter | Colorectal cancer, ovarian cancer, breast cancer, prostate cancer, bladder cancer | Promotes cancer cell growth, metastasis, stemness and chemoresistance (c-Myc, Wnt/β-catenin signaling, glycolysis, HIF1α) |
| KDM3C | JHDMA2C, JMD1C | Promoter | Esophageal cancer, colorectal cancer | Promotes cancer cell proliferation and metastasis (YAP1 signaling, ATF-2) |
| KDM4A | JHDMA3A, JMD2A | Promoter | Breast cancer, liver cancer | Promotes cancer progression through repression of the tumor suppressor ARHI (miR372) Downregulated in cancer tissues and significantly decreases as cancer progresses |
| KDM4B | JMD2B | Promoter | Breast cancer, gastric cancer, ovarian cancer, colorectal cancer, prostate cancer | Promotes EMT and metastasis, and regulates the seeding and growth of peritoneal tumors involved in resistance to PI3K inhibition (p-ERK, β-catenin) Promotes cancer progression (HIF-1α, miR-335-5p) |
| KDM4C | JMD2C, GASC1 | Promoter | Breast cancer, pancreatic cancer | Promotes cell proliferation and tumor growth (β-catenin) |
| KDM5A | JARID1A, RBP2 | Promoter | Breast cancer, colorectal cancer, cervical cancer | Promotes proliferative activity and invasion, and inhibition of KDM5A causes growth arrest at the G1 phase (c-Myc) |
| KDM5B | JARID1B, RBP2-like | Promoter | Colorectal cancer, lung cancer, gastric cancer | Promotes cell proliferation, metastasis, and expression of CSCs, and inhibition of KDM5B results in cell cycle arrest, apoptosis, and senescence (ER2F/ABB pathway) Overexpression of KDM5B predicts therapy failure and is associated with cancer cell growth, migration and invasion Inhibits the multidrug resistance of colon cancer cell lines by downregulating ABCC1 |
| KDM5D | JARID1D, SMCY | Promoter | Gastric cancer | Promotes cell proliferation and EMT |
| **KDM6/UT** | | | | |
| KDM6A | UTX | Promoter | Breast cancer | Promotes cell proliferation and invasiveness KDM6A loss induces squamous-like, metastatic pancreatic cancer |
| KDM6B | JMD3 | Promoter | Ovarian cancer, breast cancer, gastric cancer | High expression of KDM6B is correlated with poor prognosis |
| KDM6C | UTY | Promoter | Bladder cancer | UTY-knockout cells have increased cell proliferation compared to wild-type cells |
Histone demethylases. The identification of histone demethylases (HDMs or KDMs) has lagged behind that of HMTs. Thus far, KDMs can be classified into two groups. The amine-oxidase type lysine-specific demethylases (LSDs) and the highly conserved JumonjiC (JMJC) domain-containing histone demethylases. LSD1 and LSD2, also known as KDM1A and B, are flavin adenine dinucleotide (FAD)-dependent amine oxidases that can only demethylate monomethylated and dimethylated lysine residues. LSD1 has been identified to specifically activate androgen receptor (AR) target genes along with AR by demethylating H3K9.404 The human genome codes more than 30 JMJC-containing KDMs that are able to remove methyl groups from all three methyl-lysine states. JHDM1A was the first characterized JMJC domain-containing HDM and specifically demethylates H3K36me2 and H3K36me1.405 Not all JMJC domain-containing proteins are able to demethylate histone proteins, such as HIF1AN and the transmembrane phosphatidylserine receptor PTDSR. JMJC-containing HDMs can be divided into six families:360 the JHDML, JHDMD1, JHDM3 (JMD2), JARID, PHF, and UT families. Notably, not all of these families possess the ability of histone demethylation. However, some JMJC-containing proteins, including those that are not included in these six families, contain one or more methylated-histone-binding domains. Their potential to demethylate methyl-lysine or methyl-arginine must be investigated. In addition to demethylases for lysine residues, JMJD6 is the first characterized JMJC domain-containing histone demethylase and lysine hydroxylase. It can remove methyl groups from H3R2 and H4R3.406 Another kind of protein is peptidylarginine deiminases (PADs or PADIs) or protein-arginine demethylases for lysine residues, JMJD6 is the first characterized JMJC domain-containing histone demethylase and lysine hydroxylase. It can remove methyl groups from H3R2 and H4R3.406 Another kind of protein is peptidylarginine deiminases (PADs or PADIs) or protein-arginine demethylases for lysine residues, JMJD6 is the first characterized JMJC domain-containing histone demethylase and lysine hydroxylase. It can remove methyl groups from H3R2 and H4R3.406 Another kind of protein is peptidylarginine deiminases (PADs or PADIs) or protein-arginine demethylases for lysine residues, JMJD6 is the first characterized JMJC domain-containing histone demethylase and lysine hydroxylase. 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in prostate cancer with decreased levels of H3K9me2/3 and increased levels of H3K9me1.\textsuperscript{417} H3K9me3 is thought to be a hallmark of heterochromatic areas of the genome. In addition, KDM4 family members were the first identified demethylases targeting trimethylated lysines. Aberrant expression of KDM4 family members might lead to instability of the genome and become involved in tumorigenesis.\textsuperscript{410} Members of the KDM6 family usually act as tumor suppressors and are thought to cause cell growth arrest.\textsuperscript{10} For example, the tumor suppressor proteins p16INK4A and p14ARF, encoded by the INK4A-ARF locus, are repressed by H3K27me3. When stimulated by oncogenic factors, KDM6B is recruited to the INK4A-ARF locus and activates the transcription of these two tumor suppressors.\textsuperscript{419} In colorectal cancer, KDM7C is required for the efficacy of oxaliplatin and doxorubicin and for the activation of p53.\textsuperscript{420} (Table 3).

**NONCODING RNA**

Epigenetic related noncoding RNAs (ncRNAs) include microRNAs (miRNAs), small interfering RNA (siRNAs), Piwi-interacting RNA (piRNAs), and long noncoding RNAs (lncRNAs). MiRNAs, one of the most studied ncRNAs, are small RNAs between 19 and 22 nucleotides in length that play important roles in the regulation of gene expression by controlling mRNA translation. Intriguingly, the regions that miRNAs usually target are frequently associated with carcinogenesis.\textsuperscript{505} Generally, they can be divided into tumor-promoting and tumor-suppressing miRNAs. During tumorigenesis, oncogenic miRNAs such as miR-155, miR-21 and miR-17-92 are usually overexpressed, and tumor-suppressive miRNAs such as miR-15-16 are downregulated.\textsuperscript{568} There is another type of miRNA, cellular context-dependent miRNAs, functioning in tumorigenesis. For example, miR-146 has been shown to be overexpressed in multiple cancers, whereas a recent study has proven that miR-146 can reduce the expression of BRCA1.\textsuperscript{568,569} Meanwhile, the expression of proteins and enzymes is also regulated by certain miRNAs. Mir-101 directly represses EZH2, and abnormal down-regulation of miR-101 has been observed in cancers.\textsuperscript{570,571} The expression of the miR-29 family is inversely correlated with that of the miR-101 family. Mir-29 inhibits tumorigenesis by inducing reexpression of methylation-silenced tumor suppressor genes.\textsuperscript{572} LncRNAs are another large group of noncoding RNAs that play a vital role in tumorigenesis. Some lncRNAs are cancer type-specific, such as PCGE1 in prostate cancer and H19 in hepatocellular carcinoma.\textsuperscript{573,574} Many aberrant lncRNAs have been discovered in various cancers. Dysregulation of HOTAIR has been found in lung, pancreatic, and colorectal cancer.\textsuperscript{575-577}

Therefore, ncRNAs can either be directly involved in tumorigenesis or indirectly affect tumor development by participating in other epigenetic events.

**INHIBITORS AND CLINICAL TRIALS**

Unlike genetic mutations, epigenetic alterations are reversible. Given the importance of epigenetic marks in tumorigenesis, the availability of corresponding inhibitors has attracted extensive attention. Meanwhile, epigenetic regulation of a gene usually requires more than one epigenetic event. Currently, there are six epigenetic drugs approved for clinical use by the FDA (Table 4).

Targeting DNA methylation

Blockade of DNMTs is the most effective way to prevent aberrant DNA hypermethylation. However, until now, targeting of the DNA methyltransferase enzymes still lacks specificity and even causes hypomethylation of the global genome.\textsuperscript{578} Complete deletion of DNMT1 in mice results in embryonic lethality.\textsuperscript{579} Knockout of DNMT1 in fibroblast cells causes aberrant expression of 10% of genes and p53-dependent death.\textsuperscript{580} Administration of DNA methylation inhibitors results in tumorigenesis in male Fischer rats.\textsuperscript{581} Regulation of DNA methylation is vital in cell survival and function, and in addition to the specificity needed and the side effect associated, it is hard to identify proper drugs. DNA methylation inhibitors can be divided into two groups: nucleoside analogs and nonnucleoside analogs. Nucleoside analogs have a modified cytosine ring and can be turned into nucleotides and incorporated into newly synthesized DNA or RNA. DNA methyltransferases are bound by covalent complexes with the analogs, which inhibits DNA methylation. 5-Aza-CR and 5-aza-2′-deoxycytidine (5-Aza-CdR) are currently the two most studied and promising demethylation agents.\textsuperscript{582} 5-Aza-CR and zebularine are ribonucleotide analogs that can be phosphorylated to be able to incorporate into RNA. However, they can also be incorporated into DNA via the ribonucleotide reductase pathway. 5-Azacitidine, an analog of cytidine, is an injectable suspension for the treatment of myelodysplastic syndromes (MDSs). It promotes cell differentiation, demethylation, and reexpression of inactivated genes.\textsuperscript{583} The 5-aza-2′-deoxycytidine effects include fetal abnormalities\textsuperscript{584} and decreased male fertility, especially at high doses, but its analog, 6-aza-cytidine, does not show such effects.\textsuperscript{585} Notably, after treating the noninvasive breast cancer cell lines MCF-7 and ZR-75-1 with azacitidine, the cells gained invasive abilities due to the hypomethylation of several prometastasis genes.\textsuperscript{586} Decitabine (5-Aza-CdR) and 5-fluoro-2′-deoxycytidine (5-F-CdR) are deoxyribonucleoside analogs that are capable of incorporating into DNA following phosphorylation. Decitabine (5-aza-2′-deoxycytidine) inhibits DNA methylation in a dosage-dependent manner. It can reactivate silenced genes at low doses but gains cytotoxicity at high doses, while myelosuppression is the major side effect at all doses.\textsuperscript{587} Dihydro-5-aza-cytidine (DHAC) is a biologically active and chemically stable analog of 5-azacitidine with decreased toxicity.\textsuperscript{588,589} Because of its hydrolytic stability, it may be administrated via prolonged i.v. infusion, potentially eliminating the acute toxicities caused by administration of 5-azacytidine.\textsuperscript{590} Zebularine is a potential oral DNA-demethylating drug with stability in acidic environments and in aqueous solutions.\textsuperscript{591} However, the near millimolar dose requirements and the limited bioavailability in rodents (<7%) and primates (<1%) leave zebularine far from clinical translation.\textsuperscript{592}

Among the drugs discussed, 5-Aza-CR\textsuperscript{593} and 5-Aza-CdR\textsuperscript{594} have already been approved by the US Food and Drug Administration (FDA) for the treatment of certain subtypes of MDS and chronic myelomonocytic leukemia. Because of their intrinsic preference for newly synthetic DNA, they tend to affect dividing cells, i.e., cancer cells.\textsuperscript{595} Ongoing preclinical experiments and clinical trials are exploring their efficacy in solid tumors. The common side effects of these nucleoside-like analogs are mutagenic risk and genomic instability. Nonnucleoside analogs are capable of avoiding these side effects. Currently, many nonnucleoside analogs have been developed to prevent DNA from aberrant hypermethylation. These drugs are usually small molecular inhibitors and directly target catalytic sites rather than incorporating into DNA. Based on a three-dimensional model of DNMT1, RG108 was designed to block the activity of this enzyme and cause demethylation.\textsuperscript{596} Psammaplin is a group of natural extracts from the sponge Pseudoceratina purpurea and is capable of inhibiting both DNA methyltransferases and histone deacetylases with mild cytotoxicity.\textsuperscript{597} Similarly, EGCG ((-)-epigallocatechin-3-gallate) is the major polyphenol from green tea and reversibly demethylates methyl-DNA, resulting in the reactivation of multiple key genes, including hMLH1, P16, and RA, in colon, esophageal, and prostate cancer cell lines.\textsuperscript{598} Both hydralazine and procainamide, two drugs associated with lupus-like autoimmune diseases, can inhibit DNA methylation and induce self-reactivity in cloned T-cell lines.\textsuperscript{599} They have promising tumor suppressor-reactivating and antitumor actions in breast cancer.\textsuperscript{560,601} Another...
strategy is developing antisense oligonucleotides to inhibit DNMT transcription. MG98 is a second-generation phosphorothioate antisense oligodeoxynucleotide that prevents DNMT1 mRNA translation effects but has no obvious antitumor effect.609 It has been under investigation in preclinical experiments and phase I/II clinical trials, especially in solid tumors.610,611 Of note, in a systemic analysis comparing nonnucleoside inhibitors with 5-Aza-CdR, the latter showed better efficacy in DNA demethylation inhibition.605

Table 4. Epigenetic drugs approved by the FDA.

| Compound            | Synonym                | Clinical name | Condition  | Approved year | Company                  |
|---------------------|------------------------|---------------|------------|---------------|--------------------------|
| Azacitidine         | 5-Azacitidine, 5-Aza-CR| Vidaza        | MDS        | U.S. FDA (2004)| Pharnion Corporation     |
| 5-Aza-CdR, decitabine|                        | Dacogen       | MDS        | U.S. FDA (2006)| Janssen Pharmaceuticals   |
| Suberoylanilide hydroxamic acid (SAHA) | Vorinostat | Zolinza       | CTCL       | U.S. FDA (2006) | Merck                    |
| Romidepsin          | Depsipeptide, FK-229, FR901228 | Istdox       | CTCL       | U.S. FDA (2009) | Celgene                  |
| Belinostat          | PXD101                 | Beleodaq      | PTCL       | U.S. FDA (2014) | TopoTarget               |
| Panobinostat        | LBHS89                 | Farydak       | Multiple myeloma | U.S. FDA (2015) | Novartis                 |
| Chidamide           | Tucidinostat, HBI-8000 | Epidaza      | PTCL       | China FDA (2015) | Chipscreen Biosciences   |

FDA Food and Drug Administration, MDS myelodysplastic syndrome, CTCL cutaneous T-cell lymphoma, PTCL peripheral T-cell lymphoma

strategy is developing antisense oligonucleotides to inhibit DNMT transcription. MG98 is a second-generation phosphorothioate antisense oligodeoxynucleotide that prevents DNMT1 mRNA translation effects but has no obvious antitumor effect.609 It has been under investigation in preclinical experiments and phase I/II clinical trials, especially in solid tumors.610,611 Of note, in a systemic analysis comparing nonnucleoside inhibitors with 5-Aza-CdR, the latter showed better efficacy in DNA demethylation inhibition.605

Inhibitors of histone modifications

Compared with DNA methylation, histone modifications have been investigated in broader areas of diseases, including solid tumors, hematological malignancies, and even many inflammatory diseases (such as viral infection, diabetes and inflammatory lung diseases). During the process of gene silencing, lysine deacetylation and demethylation of H3K4 rather than demethylation of H3K9 or cytosine methylation might be the primary causative event.606 Therefore, histone modification plays an essential role in the regulation of gene expression, which also makes it a promising target for disease treatment. Clinical trials targeting histone acetylation and histone methylation are listed in Table 6 and Table 7, respectively.

Inhibitors for HATs and BETs

Generally, there are two strategies for preventing aberrant histone acetylation, including altering interactions within the active sites within HATs or using mimetic products of enzymatic substrates. To date, many inhibitors targeting BRD proteins have been investigated in clinical trials, whereas there are no clinical trials investigating inhibitors for HATs.

Bisubstrate inhibitors are selective inhibitors for PCAF, p300, and Tip60. They mimic two substrates of HATs: the cofactor acetyl coenzyme A (Ac-CoA) and a peptide resembling the lysine substrate.507,608 However, due to their peptidic nature and size, they are not membrane-permeable and require the assistance of a delivery system. Based on inhibitory strategies for HATs, nonpeptide small molecular inhibitors have been developing as potential therapeutic agents. Several small molecule inhibitors are natural products, including garcinol, curcumin, and anacardic acid.609–611 These natural HAT inhibitors lack selectivity between HATs and often have other targets. Therefore, structurally modified and synthetic compounds have been reported. A-Methylene-g-butyrolactones are small molecular inhibitors of HATs with selectivity for either GCN5L2 or PCAF.612 Isothiazolone is another HAT inhibitor targeting p300 and PCAF.613 However, high reactivity towards thiolates limits the application of HAT inhibitors in biological systems. Other inhibitors of HATs, such as thiadiazolidinediones and C646, have been gradually identified and show promising effects in multiple cancers. Another strategy to inhibit HAT activity is to target protein–protein interactions between HATs and their interaction partners. This method is dependent on the function of the interactions rather than the acetylation activity of HATs. ICG-001 and PRI-724 are representatives of this kind of inhibitor. Appropriately applying HAT agonists is also important to correct aberrant acetylation during diseases. CTPB is derived from anacardic acid and selectively activates p300, resulting in gene transcription.609 TTK21 and SPV106 are two other agonists based on anacardic acid.

Binding to BRDs and blocking acetylated lysine recognition is another mechanism that inhibits acetylation. JQ1 and I-BET762 are two representative inhibitors of the BET family. JQ1 is a cell-permeable small molecule and can competitively bind to BRD4 fusion oncoproteins, such as BRD4-NUT, resulting in cancer cell differentiation and apoptosis.614 Similarly, I-BET762 is also a synthetic mimic of and competes with BRD4.615 Other compounds, such as MS417, OTX-015, RVX-208, OXFB-D, I-BET151, PFI-1, MS436, and XD14, are also BET inhibitors and have been well illustrated in other published papers.616 We will focus on the associations between these compounds and cancers. However, a number of non-BET proteins containing BRDs have attracted considerable attention. Many non-BET bromodomain inhibitors are based on a structure called the “WPF shelf” and a “gatekeeper” residue located at the start of the C helix.617 Several HATs have a BRD, such as Gcn5, PCFA, p300, and CBP. Inhibitors for CBP include MS5216, MS7972, ischemic, SGC-CBP30 and I-CBP112; optimized 1-(1H-indol-1-yl)ethanone derivatives have also shown promising results in inhibiting CBP and p300.618 BAZ2A/B bromodomain inhibitors include BAZ2-ICR and GSK2801. The quinolone-fused lactam LP99 was the first synthetic selective inhibitor for BRD7/9. I-BRD9 was identified by GlaxoSmithKline (GSK) and is a selective inhibitor of BRD9, which has more than 200-fold selectivity for BRD9 over BRD7 and 700-fold selectivity for BRD9 over BET family members.619 PFI-3 is a potential inhibitor of SMARCA4 and P81 with a stronger affinity for the bromodomain of SMARCA4. However, Vangamudi et al. identified that the ATPase domain within SMARCA4 bypassed the anticancer effects related to the bromodomain since PFI-3 did not inhibit cell proliferation.620 The BRPF1 (bromodomain and PHD finger-containing 1) protein is part of the BRPF family, which is a component of MYST family complexes. The inhibitors of BRPF1 include PFI-4, OF-1, and NI-57. 1,3-Dimethyl benzimidazolones were the first selective inhibitors of BRPF1. PFI-4 and OF-1 are two close analogs of 1,3-dimethyl benzimidazolone that have been identified by the Structural Genomics Consortium (SGC). Another BRPF1 inhibitor, NI-57, was discovered by the SGC based on a new quinolinone scaffold. Both NI-57 and OF-1 are thought to interact
| Condition | Design | Sample size | Phase | Current status | NCT          |
|-----------|--------|-------------|-------|----------------|--------------|
| **Azacitidine (5-azacitidine)-based trials** | | | | | |
| High-risk MDS | Azacitidine | 44 | IV | Completed | NCT01201811 |
| Low-risk MDS | Azacitidine | 216 | III | Active, not recruiting | NCT01566695 |
| High-risk MDS | Azacitidine | 358 | III | Completed | NCT00071799 |
| CML | Azacitidine | 11 | II | Completed | NCT01350947 |
| AML, MDS | Azacitidine | 187 | III | Completed | NCT00887068 |
| Relapsed or refractory T-cell lymphoma | Azacitidine | 20 | III | Recruiting | NCT03703375 |
| AML with complete remission | Azacitidine | 472 | III | Active, not recruiting | NCT01757535 |
| Recurrent IDH1/2-mutated glioma | Azacitidine | 63 | II | Not yet recruiting | NCT03666559 |
| Prostate cancer | Azacytidine | 36 | II | Completed | NCT00384839 |
| Head and neck squamous cell carcinoma | Azacitidine | 25 | II | Recruiting | NCT02178072 |
| Locally advanced or metastatic nasopharyngeal carcinoma | Azacitidine | 36 | II | Completed | NCT02269943 |
| Pancreatic cancer | Azacitidine | 80 | II | Recruiting | NCT01845805 |
| Solid tumors and hematological disorders | Azacitidine | 125 | II | Recruiting | NCT02494258 |
| AML | Azacitidine + venetoclax | 42 | II | Recruiting | NCT03466294 |
| AML | Azacitidine + venetoclax | 30 | II | Recruiting | NCT03573024 |
| AML | Azacitidine + venetoclax | 400 | III | Recruiting | NCT02993523 |
| AML, MDS | Azacitidine + eltrombopag | 25 | II | Completed | NCT01488565 |
| MDS | Azacitidine + eltrombopag | 356 | III | Terminated | NCT02158936 |
| MDS | Azacitidine + APR-246 | 156 | III | Recruiting | NCT03745716 |
| AML, MDS | Azacitidine + DLI | 30 | II | Completed | NCT01541280 |
| AML/MDS | Azacitidine + lenalidomide | 72 | II | N/A | NCT01556477 |
| High-risk MDS with 5q deletion | Azacitidine + lenalidomide | 50 | II | Completed | NCT01088373 |
| AML | Azacitidine + lenalidomide | 88 | II | Completed | NCT01358734 |
| Elderly patients with AML | Azacitidine + lenalidomide | 120 | II | Completed | NCT01301820 |
| Refractory AML | Azacitidine + lenalidomide | 37 | II | Completed | NCT01743859 |
| MDS, CMML and AML relapsing after allo-HSCT | Azacitidine + lenalidomide + DLI | 50 | II | Active, not recruiting | NCT02472691 |
| MDS with excess blasts 2 | Azacitidine + vosaroxin | 168 | II | Recruiting | NCT03338348 |
| AML | Azacitidine vs conventional care regimen | 488 | III | Completed | NCT01074047 |
| AML, MDS with FLT3-ITD mutation | Azacitidine + sorafenib | 17 | II | Completed | NCT02196857 |
| Advanced solid tumors | Azacitidine + durvalumab | 60 | II | Recruiting | NCT02811497 |
| High-risk MDS, AML | Azacitidine + durvalumab | 213 | II | Active, not recruiting | NCT02775903 |
| MDS patients with excess blasts, progressing | Azacitidine + rigosertib | 67 | III | Active, not recruiting | NCT01928537 |
| AML, MDS, CML | Azacitidine + HAG regimen | 120 | III | Not yet recruiting | NCT01056211 |
| AML with NPM1 mutation | Azacitidine + sorafenib | 17 | II | Completed | NCT02196857 |
| Refractory or relapsed AML | Azacitidine + lirilumab | 37 | II | Completed | NCT02399917 |
| AML | Azacitidine + induction therapy | 336 | II | N/A | NCT01180322 |
| AML with NPM1 mutation | Azacitidine + pembrolizumab | 28 | II | Not yet recruiting | NCT03769532 |
| Pancreatic cancer | Azacitidine + pembrolizumab | 31 | II | Recruiting | NCT03264404 |
| Metastatic melanoma | Azacitidine + pembrolizumab | 71 | II | Recruiting | NCT02816021 |
| MDS | Azacitidine + pembrolizumab | 40 | II | Recruiting | NCT03094637 |
| Chemorefractory metastatic colorectal cancer | Azacitidine + pembrolizumab | 31 | II | Active, not recruiting | NCT02260440 |
| Advanced or metastatic non-small-cell lung cancer | Azacitidine + pembrolizumab | 100 | II | Active, not recruiting | NCT02546986 |
| Platinum-resistant ovarian cancer | Azacitidine + pembrolizumab | 20 | II | Recruiting | NCT02900560 |
| MDS | Azacitidine + lintuzumab | 7 | II | Terminated | NCT00997243 |
| Prostate cancer | Azacitidine + ATRA | 20 | II | Recruiting | NCT03572387 |
| Recurrent or refractory disease with IDH2 mutation | Azacitidine + enasidenib | 50 | II | Recruiting | NCT03683433 |
| High-risk MDS with IDH2 mutation | Azacitidine + enasidenib | 105 | II | Recruiting | NCT03383575 |
| Elderly patients with AML | Azacitidine + standard therapy | 214 | II | Completed | NCT00915252 |
| Condition                                                                 | Design                                             | Sample size | Phase | Current status                  | NCT     |
|---------------------------------------------------------------------------|----------------------------------------------------|-------------|-------|---------------------------------|---------|
| Refractory or relapsed AML                                               | Azacitidine + avelumab                             | 52          | I/II  | Recruiting                      | NCT02953561 |
| AML, MDS, CML                                                             | Azacitidine + pevonedistat                         | 450         | III   | Recruiting                      | NCT03268954 |
| Relapsed or refractory AML                                               | Azacitidine + pevonedistat                         | 72          | II    | Not yet recruiting              | NCT03745352 |
| High-risk MDS, AML, CML                                                   | Azacitidine + pevonedistat                         | 120         | II    | Active, not recruiting          | NCT02610777 |
| AML without remission after allogeneic stem cell transplantation          | Azacitidine + pevonedistat                         | 30          | II    | Recruiting                      | NCT03709576 |
| MDS                                                                       | Azacitidine + pevonedistat                         | 71          | II    | Recruiting                      | NCT03238248 |
| Elderly patients with AML                                                 | Azacitidine + gemtuzumab ozogamicin                | 133         | II    | Active, not recruiting          | NCT00658814 |
| Recurrent and resectable osteosarcoma                                     | Azacitidine + nivolumab                           | 51          | I/II  | Not yet recruiting              | NCT03628209 |
| Childhood relapsed/refractory AML                                         | Azacitidine + nivolumab                           | 26          | II    | Not yet recruiting              | NCT03825367 |
| Elderly patients with AML or high-risk MDS                               | Azacitidine/decitabine + nivolumab or midostaur    | 1670        | II/III| Suspended                       | NCT03092674 |
| Refractory/refractory AML                                                | Azacitidine + ipilimumab + nivolumab              | 182         | II    | Recruiting                      | NCT02397720 |
| MDS                                                                       | Azacitidine + nivolumab + ipilimumab               | 120         | II    | Recruiting                      | NCT02530463 |
| MDS, myeloproliferative neoplasm                                          | Azacitidine + ruxolitinib Phosphate                | 123         | II    | Completed                       | NCT01787487 |
| Relapsed or refractory AML, MDS                                           | Azacitidine + quinaz uninib                      | 72          | II    | Recruiting                      | NCT01892371 |
| AML                                                                       | Azacitidine vs fludarabine + cytarabine            | 289         | III   | Active, not recruiting          | NCT02319135 |
| AML, high-risk MDS                                                        | Azacitidine + cytarabine + tosedostat              | 96          | II    | Active, not recruiting          | NCT01636609 |
| Peripheral T-cell lymphoma                                                | Azacitidine + CHOP                                 | 20          | II    | Recruiting                      | NCT03542266 |
| AML                                                                       | Azacitidine + intensive chemotherapy              | 720         | III   | Recruiting                      | NCT03416179 |
| Advanced non-small-cell lung cancer                                       | Azacitidine + paclitaxel                           | 240         | II    | Active, not recruiting          | NCT02250326 |
| Decitabine (5-aza-2′deoxycytidine)-based trials                          |                                                    |             |       |                                 |          |
| Refractory CML                                                            | Decitabine                                         | 40          | II    | Completed                       | NCT00042003 |
| Metastatic papillary thyroid cancer or follicular thyroid cancer           | Decitabine                                         | 12          | II    | Completed                       | NCT00085293 |
| AML with TP53 mutation                                                    | Decitabine                                         | 60          | II    | Recruiting                      | NCT03063203 |
| AML                                                                       | Decitabine                                         | 546         | II    | Completed                       | NCT00416598 |
| MDS                                                                       | Decitabine                                         | 128         | II    | Completed                       | NCT00067808 |
| Elderly patients with AML                                                 | Decitabine                                         | 238         | II    | Completed                       | NCT00866073 |
| Advanced-stage MDS                                                       | Decitabine                                         | 160         | III   | Completed                       | NCT00043381 |
| Relapse and refractory diffuse large B-cell lymphoma                      | Decitabine                                         | 60          | IV    | Recruiting                      | NCT03579082 |
| Relapsed or refractory T lymphoblastic lymphoma                           | Decitabine                                         | 40          | IV    | Recruiting                      | NCT03558412 |
| CML                                                                       | Decitabine + imatinib mesylate                      | 80          | II    | Completed                       | NCT00054431 |
| High-risk MDS, AML                                                        | Decitabine + tosedostat                            | 34          | II    | Completed                       | NCT01567059 |
| Metastatic castration-resistant prostate cancer                           | Decitabine + enzalutamide                          | 21          | I/II  | Not yet recruiting              | NCT03709550 |
| Peripheral T-cell lymphoma                                                | Decitabine + CHOP                                  | 100         | III   | Not yet recruiting              | NCT03553537 |
| Relapsed FLT3-ITD-mutated AML, MDS                                        | Decitabine + quinaz uninib                        | 52          | II    | Recruiting                      | NCT03661307 |
| AML                                                                       | Decitabine + clofarabine                           | 727         | II    | Active, not recruiting          | NCT02085408 |
| AML                                                                       | Decitabine + ruxolitinib Phosphate                 | 42          | I/II  | Recruiting                      | NCT02257138 |
| AML                                                                       | Decitabine + bortezomib                            | 165         | II    | Active, not recruiting          | NCT01420926 |
| AML                                                                       | Decitabine + cytarabine + daunorubicin hydrochloride| 180        | II    | Active, not recruiting          | NCT01627041 |
with BRPF1-3 as pan-BRPF bromodomain inhibitors. Based on the bromodomain contained within both TRIM24 (tripartite motif containing protein 24) and BRPF1, a dual inhibitor, IACS-9571, has been identified.\textsuperscript{621} Bromosporine is a panbromodomain inhibitor with good cellular activity, whereas in a recent study, researchers noticed that bromodomain inhibitors only targeted the BET family rather than other BRDs.\textsuperscript{622}

\textit{Inhibition of HDACs.} Given that multiple methods can regulate HDAC activity, the designation of HDAC inhibitors has its own advantages. In the 1970s, butyrate was found to induce the accumulation of acetylated histones in cancer cells, which is thought to be associated with the inhibition of deacetylation.\textsuperscript{623} Later, a natural extract, trichostatin A (TSA), was identified to inhibit the activity of partially purified HDACs and induce cancer cell differentiation and apoptosis.\textsuperscript{624} Gradually, more natural and synthetic compounds have been identified to inhibit histone deacetylation. A study reported that administration of HDAC inhibitors only regulates a small number of genes (1–2%) but induces an obvious and rapid decrease in c-Myc gene expression, which indicated that a restricted set of cellular genes was uniquely sensitive to regulation of histone acetylation.\textsuperscript{625} The combination of two HDAC inhibitors, SAHA and TSA, induced melanoma cell growth arrest by upregulating p21, p27 and NF-kB, and MG132 can enhance the effect of TSA.\textsuperscript{626} The inhibition of HDACs has been investigated in various cancers, with promising antitumor effects.\textsuperscript{627,628} Based on the characteristics of their chemical structures, HDAC inhibitors can be divided into five groups: short-chain fatty acids, hydroxamic acids, benzamides, cyclic peptides, and hybrid molecules. In addition to those included in the five groups, some new synthetic compounds also act as inhibitors of HDACs.

The short-chain fatty acid group contains sodium butyrate, valproic acid (VPA), sodium phenylbutyrate, and AN-9 (pivaloyloxymethyl butyrate). The effective concentration of butyrate is usually at the micromolar level. The group of hydroxamic acids includes more than ten members and is the best-studied class. Some common HDAC inhibitors are nivalanilide (HMBA) and saframycin A (SAFMA). In addition to these, many other synthetic compounds are classified as HDAC inhibitors. The mechanisms of many of these inhibitors are similar or different from the two HDAC inhibitors, SAHA and TSA, used in previous studies. The combination of two HDAC inhibitors, SAHA and TSA, induced melanoma cell growth arrest by upregulating p21, p27 and NF-kB, and MG132 can enhance the effect of TSA.\textsuperscript{626} The inhibition of HDACs has been investigated in various cancers, with promising antitumor effects.\textsuperscript{627,628} Based on the characteristics of their chemical structures, HDAC inhibitors can be divided into five groups: short-chain fatty acids, hydroxamic acids, benzamides, cyclic peptides, and hybrid molecules. In addition to those included in the five groups, some new synthetic compounds also act as inhibitors of HDACs.

### Table 5 continued

| Condition | Design | Sample size | Phase | Current status | NCT |
|-----------|--------|-------------|-------|---------------|-----|
| AML | Guadecitabine | 815 | III | Completed | NCT02348489 |
| Philadelphia-negative MDS | Guadecitabine | 50 | II | Recruiting | NCT01896586 |
| High-risk MDS | Guadecitabine | 103 | II | Recruiting | NCT03075826 |
| Advanced hepatocellular carcinoma (HCC) | Guadecitabine | 51 | II | Completed | NCT02131597 |
| AML, MDS | Guadecitabine | 401 | II | Recruiting | NCT01752933 |
| MDS, CMML | Guadecitabine | 408 | III | Recruiting | NCT02907359 |
| AML, MDS | Guadecitabine + DLI | 40 | II | Not yet recruiting | NCT03576963 |
| MDS relapsing post AlloSCT | Guadecitabine + DLI | 90 | II | Recruiting | NCT02684162 |
| Refractory metastatic colorectal cancer | Guadecitabine + nivolumab | 45 | II | Not yet recruiting | NCT03576963 |
| Recurrent ovarian, primary peritoneal, or fallopian tube cancer | Guadecitabine + Pembrolizumab | 38 | II | Recruiting | NCT02901899 |
| Metastatic colorectal cancer | Guadecitabine + irinotecan | 108 | II | Active, not recruiting | NCT03308396 |
| Advanced kidney cancer | Guadecitabine + durvalumab | 58 | I/II | Recruiting | NCT03179943 |
| Refractory or resistant urothelial carcinoma | Guadecitabine + atezolizumab (anti-PD-L1 antibody) | 53 | II | Recruiting | NCT02935361 |
| Advanced MDS CMML | Guadecitabine + atezolizumab | 72 | I/II | Recruiting | NCT03206047 |
| Recurrent ovarian, fallopian tube, or primary peritoneal cancer | Guadecitabine + CDX-1401 Vaccine + atezolizumab | 75 | I/II | Recruiting | NCT01696032 |
| Ovarian cancer | Guadecitabine + carboplatin | 120 | II | Recruiting | NCT00359606 |
| 5-F-CdR-based trials | Guadecitabine + Pembrolizumab | 38 | II | Recruiting | NCT02901899 |
| Advanced cancer | 5-Fluoro-2-deoxyctydine (FdCyd) | 58 | I | Completed | NCT00359606 |
| Hydralazine-based trials | Guadecitabine + Pembrolizumab | 38 | II | Recruiting | NCT02901899 |
| Ovarian cancer | Hydralazine + valproate | 211 | III | N/A | NCT00532818 |
| Cervical cancer | Hydralazine + valproate | 143 | III | N/A | NCT03033299 |
| Recurrent-persistent cervical cancer | Hydralazine + valproate | 230 | III | N/A | NCT02446652 |
| Cervical cancer | Hydralazine + erlotinib | 18 | II | Recruiting | NCT00404326 |
| Refractory solid tumors | Hydralazine + magnesium valproate | 15 | II | Recruiting | NCT00404508 |

Venetoclax, Bcl-2-selective inhibitor; Eltrombopag, c-mpl (TpoR) receptor agonist; APR-246, p53 agonist; DLI, donor leukocyte infusion; lenalidomide, derivative of thalidomide; sorafenib, multiple tyrosine kinase inhibitor; durvalumab, anti-PD-L1 monoclonal antibody; rigosertib, Ras mimetic; HAG regimen, homoharringtonine + cytarabine + G-CSF; lirilumab, anti-KIR monoclonal antibody; pembrolizumab, anti-PD-1 monoclonal antibody; lintuzumab, anti-CD33 monoclonal antibody; enasidenib, IDH2 inhibitor; avelumab, anti-PD-L1 monoclonal antibody; pevonedistat, NEDD8 inhibitor; nivolumab, anti-PD-1 monoclonal antibody; sirolimus, MTOR inhibitors; AG-120, IDH1 inhibitor; rituximab, anti-CD20 monoclonal antibody; PKC412, multitargeted protein kinase inhibitor; birinapant, SMAC mimetic antagonist; sonidegib, Hedgehog signaling pathway inhibitor; PF-04449913 (glasdegib), Hedgehog signaling pathway inhibitor; etanercept, TNF inhibitor; ruxolitinib phosphate, JAK inhibitor; quizartinib, tyrosine kinase inhibitor; tosedostat, inhibitor of the M1 family of aminopeptidases; atezolizumab, anti-PD-L1 monoclonal antibody.
| Condition | Design | Sample size | Phase  | Current status | NCT          |
|-----------|--------|-------------|--------|----------------|--------------|
| Anti-HDAC |        |             |        |                |              |
| Valproic acid-based trials |        |             |        |                |              |
| Advanced thyroid cancers | Valproic acid | 13 | II | Completed | NCT01182285 |
| Uveal melanoma | Valproic acid | 150 | II | Recruiting | NCT02068586 |
| Pancreatic cancer | Valproic acid | 20 | II | N/A | NCT01333631 |
| Non-Hodgkin lymphoma, Hodgkin lymphoma | Valproic acid | 52 | II | N/A | NCT01016990 |
| Locally advanced head and neck squamous cell carcinoma | Valproic acid + platinum-based chemoradiation | 14 | II | Completed | NCT01695122 |
| Non-small-cell lung cancer | Valproic acid + lidocaclipaplatinum-based chemoradiation | 20 | I/II | N/A | NCT01203735 |
| Recurrent high-grade glioma | Valproic acid + sildenaclipitate + sorafenib tosylate | 66 | II | Recruiting | NCT01817751 |
| Glioma | Valproic acid + levetiracetam | 120 | IV | Recruiting | NCT03048084 |
| Virus-associated cancer | Valproic acid + avelumab | 39 | II | Recruiting | NCT03357757 |
| Colorectal cancer | Valproic acid + radiation therapy | 152 | I/II | N/A | NCT01898104 |
| Refractory or relapsing small-cell lung cancer | Valproic acid + doxorubicin, cyclophosphamide and vindesine | 64 | II | Completed | NCT00759824 |
| High-grade gliomas, brain tumors | Valproic acid + temozolomide + radiation therapy | 43 | II | Completed | NCT00302159 |
| High-grade gliomas or diffuse intrinsic pontine glioma | Valproic acid + radiation | 38 | II | Active, not recruiting | NCT00879437 |
| Advanced malignant neoplasm | Valproic acid + bevacizumab + temsirolimus | 216 | I | Recruiting | NCT01552434 |
| Malignant mesothelioma | Valproic acid + doxorubicin | 45 | II | Completed | NCT00634205 |
| Diffuse large B-cell lymphoma | Valproic acid + rituximab + CHOP | 50 | I/II | Completed | NCT01622439 |
| Sodium phenylbutyrate-based trials |        |             |        |                |              |
| Progressive or recurrent brain tumors | Phenylbutyrate | 120 | II | Completed | NCT00006450 |
| Relapsed or refractory Epstein-Barr virus-positive cancer | Phenylbutyrate + valganciclovir | 14 | II | N/A | NCT00387530 |
| Refractory or relapsed AML | Phenylbutyrate + dexamethasone + sargramostim | N/A | II | Completed | NCT00006240 |
| AN-9 (pivaloyloxymethyl butyrate)-based trials |        |             |        |                |              |
| Advanced non-small-cell lung cancer | Pivanex + docetaxel | 225 | II | Completed | NCT00073385 |
| Phenylacetate-based trials |        |             |        |                |              |
| Children with recurrent or progressive brain tumors | Phenylacetate | N/A | II |              | NCT00003241 |
| Vorinostat (SAHA)-based trials |        |             |        |                |              |
| Advanced cancer | Vorinostat | 143 | I | Active, not recruiting | NCT01266057 |
| BRAFV600-mutated advanced melanoma | Vorinostat | 22 | I/II | Recruiting | NCT02836548 |
| Breast cancer | Vorinostat | 49 | I/II | N/A | NCT00416130 |
| Advanced, metastatic soft tissue sarcoma | Vorinostat | 40 | II | Completed | NCT00918489 |
| AML | Vorinostat | 37 | II | Completed | NCT00305773 |
| Advanced non-small-cell lung cancer | Vorinostat | 16 | II | Completed | NCT00138203 |
| Recurrent or persistent ovarian epithelial or primary peritoneal cavity cancer | Vorinostat | 60 | II | Completed | NCT00132067 |
| Advanced adenoid cystic carcinoma | Vorinostat | 30 | II | Completed | NCT01175980 |
| Advanced thyroid cancer | Vorinostat | 19 | II | Completed | NCT00134043 |
| Kidney cancer | Vorinostat | 14 | II | Completed | NCT00278395 |
| Metastatic or unresectable melanoma | Vorinostat | 32 | II | Completed | NCT00121225 |
| Low-grade non-Hodgkin lymphoma | Vorinostat | 37 | II | Completed | NCT00253630 |
| Progressive glioblastoma multiforme | Vorinostat | 103 | II | Completed | NCT00238303 |
| Progressive metastatic prostate cancer | Vorinostat | 29 | II | Completed | NCT00330161 |
| Advanced cutaneous T-cell lymphoma | Vorinostat | 74 | II | Completed | NCT00091559 |
| Advanced malignant pleural mesothelioma | Vorinostat | 662 | III | Completed | NCT00128102 |
| Metastatic or recurrent gastric cancer | Vorinostat + capcitabine + cisplatin | 45 | I/II | Completed | NCT01045538 |
| Breast cancer | Vorinostat + tamoxifen | 43 | II | Completed | NCT00365599 |
| T-cell non-Hodgkin lymphoma | Vorinostat + CHOP | 14 | I/II | Completed | NCT00787527 |
| Advanced non-small-cell lung cancer | Vorinostat + bortezomib | 18 | II | Completed | NCT00798720 |
| Relapsed or refractory multiple myeloma | Vorinostat + bortezomib | 143 | II | Completed | NCT00773838 |
| Recurrent glioblastoma multiforme | Vorinostat + bortezomib | 44 | II | Completed | NCT00641706 |
| Advanced soft tissue sarcoma | Vorinostat + bortezomib | 16 | II | Completed | NCT00937495 |
### Table 6 continued

| Condition                                      | Design                                      | Sample size | Phase | Current status | NCT            |
|------------------------------------------------|---------------------------------------------|-------------|-------|----------------|----------------|
| Multiple myeloma                               | Vorinostat + bortezomib                    | 637         | III   | Completed      | NCT00773747    |
| Unresectable or metastatic kidney cancer       | Vorinostat + bevacizumab                   | 37          | I/II  | Completed      | NCT00324870    |
| Glioblastoma multiforme                        | Vorinostat + temozolomide + radiation      | 125         | I/II  | Active, not recruiting | NCT00731731    |
| Diffuse intrinsic pontine glioma               | Vorinostat + radiation therapy             | 80          | I/II  | Active, not recruiting | NCT01189266    |
| Recurrent ovarian cancer                        | vorinostat + paclitaxel + carboplatin      | 70          | II    | N/A            | NCT00772978    |
| Stage IV non-small-cell lung cancer (NSCLC)    | Vorinostat + pembrolizumab                 | 100         | I/II  | Recruiting     | NCT02638090    |
| CLL, small lymphocytic lymphoma                 | Vorinostat + fludarabine phosphate +      | 40          | I/II  | Active, not recruiting | NCT00918723    |
| Relapse/refractory AML                          | Vorinostat + temozolomide                  | 23          | II    | Completed      | NCT01550224    |
| Stage II, III, or IV diffuse large B-cell lymphoma | Vorinostat + rituximab                     | 83          | II    | Active, not recruiting | NCT00972478    |
| Metastatic breast cancer                        | Vorinostat + paclitaxel + bevazcizumab     | 54          | I/II  | Completed      | NCT00368875    |
| High-grade glioma                               | Vorinostat + radiation therapy             | 101         | I/II  | Completed      | NCT01236560    |
| High-risk MDS, AML                              | Vorinostat + idarubicin + cytarabine       | 106         | II    | Completed      | NCT00656617    |
| Colorectal cancer                               | Vorinostat + hydroxycloroquine             | 76          | II    | Recruiting     | NCT02316430    |
| Advanced non-small-cell lung cancer             | Vorinostat + carboplatin + paclitaxel      | 94          | II    | Completed      | NCT00481078    |
| Metastatic colorectal cancer                    | Vorinostat + fluorouracil + leucovorin calcium | 58      | II    | Completed      | NCT00942266    |
| Recurrent glioblastoma multiforme (GBM)         | Vorinostat + isotretinoin + temozolomide   | 135         | I/II  | Active, not recruiting | NCT00555399    |
| Breast cancer                                   | Vorinostat + carboplatin + nab-paclitaxel  | 68          | II    | Completed      | NCT00616967    |
| Diffuse large B-cell non-Hodgkin lymphoma       | Vorinostat + chemotherapy + rituximab      | 107         | I/II  | Active, not recruiting | NCT01193842    |
| Advanced sarcoma                                | Vorinostat + gemcitabine + docetaxel       | 67          | II    | Recruiting     | NCT01879085    |
| AML                                            | Vorinostat + cytarabine + daunorubicin     | 754         | III   | Completed      | NCT01802333    |
| Neuroblastoma                                   | Vorinostat = 131I-MIBG                      | 105         | II    | Recruiting     | NCT02035137    |
| Multiple myeloma                                | Vorinostat + lenalidomide                  | 4420        | III   | Active, not recruiting | NCT01554852    |
| Relapsed/refractory cutaneous T-cell lymphoma (CTCL) | Vorinostat vs KW-0761                      | 372         | III   | Active, not recruiting | NCT01728805    |

**TSA (Trichostatin A)-based trials**

| Trichostatin A                                  | 42          | I      | Recruiting | NCT03838926    |

**Belinostat (PAHA, PXD101)-based trials**

| Advanced solid tumors or lymphoma               | Belinostat   | 121     | I      | Completed      | NCT00413075    |
| Relapsed or refractory peripheral T-cell lymphoma | Belinostat   | 129     | I      | Completed      | NCT00865969    |
| Liver cancer                                    | Belinostat   | 54      | I/II   | Completed      | NCT00321594    |
| MDS                                            | Belinostat   | 21      | II     | Completed      | NCT00357162    |
| Relapsed or refractory aggressive B-cell non-Hodgkin lymphoma | Belinostat   | 22      | II     | Completed      | NCT00303953    |
| Advanced multiple myeloma                       | Belinostat   | 25      | II     | Completed      | NCT00131261    |
| Solid tumors or hematological malignancies     | Belinostat + warfarin | 27     | I      | Completed      | NCT01317927    |
| Soft tissue sarcomas                            | Belinostat + doxorubicin                    | 41        | I/II   | Completed      | NCT00878800    |
| Relapsed/refractory NHL                         | Belinostat + carfilzomib                    | 19        | I      | Completed      | NCT02142530    |
| Relapsed or refractory AML, MDS                 | Belinostat + pevonedistat                   | 45        | I      | Not yet recruiting | NCT03772925    |
| Adult T-cell leukemia-lymphoma                  | Belinostat + idarubicin + cytarabine        | 20        | II     | Recruiting     | NCT02737046    |
| Recurrent ovarian epithelial cancer             | Belinostat + carboplatin                    | 29        | II     | Completed      | NCT00993616    |
| Stage IV non-small-cell lung cancer (NSCLC)     | Belinostat + carboplatin + paclitaxel       | 23        | II     | Completed      | NCT01310244    |
| Ovarian cancer                                  | Belinostat + carboplatin + paclitaxel       | 80        | I/II   | Completed      | NCT00421889    |
| Cancer of unknown primary site                  | Belinostat + carboplatin + paclitaxel       | 89        | II     | Completed      | NCT00873119    |

**Entinostat (MS-275)-based trials**

| Entinostat                                     | 49          | II     | Completed | NCT00866333    |
| MDS, AML, ALL                                   | Entinostat   | 24      | II     | Completed      | NCT00462605    |
| Metastatic melanoma                             | Entinostat   | 28      | II     | Completed      | NCT00185302    |
| Advanced breast cancer                          | Entinostat   | 512     | III    | Recruiting     | NCT03538171    |
| Metastatic kidney cancer                        | Entinostat + aldesleukin                    | 45        | I/II   | Active, not recruiting | NCT01038778    |
| TN breast cancer                                | Entinostat + atezolizumab                   | 88        | I      | Active, not recruiting | NCT02708680    |
| Advanced epithelial ovarian cancer              | Entinostat +avelumab                         | 140       | II     | Active, not recruiting | NCT02915523    |
| Metastatic colorectal cancer                    | Entinostat + regorafenib + hydroxycloroquine | 44        | II     | Recruiting     | NCT03215264    |
| Advanced renal cell carcinoma                   | Entinostat + bevacizumab + atezolizumab     | 62        | II     | Recruiting     | NCT03024437    |
| Endometrioid endometrial cancer                 | Entinostat + medroxyprogesterone acetate    | 50        | II     | Active, not recruiting | NCT03018249    |
| Condition                                                                 | Design                                                                 | Sample size | Phase | Current status          | NCT            |
|---------------------------------------------------------------------------|-------------------------------------------------------------------------|-------------|-------|-------------------------|----------------|
| Renal cell carcinoma                                                     | Entinostat + IL-2                                                       | 46          | II    | Recruiting              | NCT03501381    |
| NSCLC, melanoma, and colorectal cancer                                   | Entinostat + pembrolizumab                                             | 202         | I/II  | Active, not recruiting  | NCT02437136    |
| Relapsed and refractory lymphomas                                        | Entinostat + pembrolizumab                                             | 78          | II    | Recruiting              | NCT03179930    |
| Stage III/IV melanoma                                                    | Entinostat + pembrolizumab                                             | 14          | II    | Recruiting              | NCT03765229    |
| High-risk refractory malignancies                                        | Entinostat + nivolumab                                                | 128         | I/II  | Not yet recruiting      | NCT03838042    |
| Metastatic cholangiocarcinoma and pancreatic adenocarcinoma              | Entinostat + nivolumab                                                | 54          | II    | Recruiting              | NCT03250273    |
| Renal cell carcinoma                                                     | Entinostat + nivolumab + ipilimumab                                   | 53          | II    | Recruiting              | NCT03552380    |
| Advanced breast cancer                                                   | Entinostat + exemestane                                               | 130         | II    | Completed               | NCT00676663    |
| Breast cancer                                                             | Entinostat + exemestane                                               | 600         | III   | Active, not recruiting  | NCT02115282    |
| Advanced NSCLC                                                            | Entinostat + erlotinib                                                | 132         | I/II  | Recruiting              | NCT00602030    |
| Non-small-cell lung carcinoma                                            | Entinostat + erlotinib                                                | 70          | II    | Completed               | NCT00750698    |
| **Panobinostat (LBH589)-based trials**                                   |                                                                        |             |       |                         |                |
| High-risk MDS, AML                                                        | Panobinostat                                                           | 62          | I/II  | Active, not recruiting  | NCT01451268    |
| Advanced hematological malignancies                                      | Panobinostat                                                           | 175         | I/II  | Completed               | NCT00621244    |
| Metastatic thyroid cancer                                                | Panobinostat                                                           | 13          | II    | Completed               | NCT01013597    |
| Advanced soft tissue sarcoma                                             | Panobinostat                                                           | 53          | II    | Completed               | NCT01136499    |
| Refractory prostate cancer                                               | Panobinostat                                                           | 35          | II    | Completed               | NCT00667862    |
| Refractory clear cell renal carcinoma                                     | Panobinostat                                                           | 20          | II    | Completed               | NCT00550277    |
| Relapsed/refractory classical Hodgkin lymphoma                           | Panobinostat                                                           | 129         | II    | Completed               | NCT00742027    |
| Refractory colorectal cancer                                             | Panobinostat                                                           | 29          | II    | Completed               | NCT00690677    |
| HER2-negative locally recurrent or metastatic breast cancer              | Panobinostat                                                           | 54          | II    | Completed               | NCT00777049    |
| Relapsed and bortezomib-refractory multiple myeloma                      | Panobinostat                                                           | 55          | II    | Completed               | NCT01083602    |
| Relapsed or refractory non-Hodgkin lymphoma                              | Panobinostat                                                           | 41          | II    | Active, not recruiting  | NCT01261247    |
| Refractory CML                                                           | Panobinostat                                                           | 27          | II/III| Completed              | NCT00449761    |
| Refractory/resistant cutaneous T-cell lymphoma                           | Panobinostat                                                           | 9           | II/III| Completed              | NCT00490776    |
| Refractory CML                                                           | Panobinostat                                                           | 29          | II/III| Completed              | NCT00451035    |
| Refractory cutaneous T-cell lymphoma                                      | Panobinostat                                                           | 139         | II/III| Completed              | NCT00425555    |
| Hodgkin lymphoma (HL)                                                    | Panobinostat                                                           | 41          | III   | Completed               | NCT01034163    |
| Relapsed/refractory multiple myeloma                                     | Panobinostat + carfilzomib                                            | 80          | I/II  | Active, not recruiting  | NCT01496118    |
| Recurrent high-grade glioma                                              | Panobinostat + bevacinuzumab                                          | 51          | I/II  | Completed               | NCT00859222    |
| Recurrent prostate cancer after castration                               | Panobinostat + bicalutamide                                           | 52          | I/II  | Completed               | NCT00878436    |
| AML                                                                       | Panobinostat + idarubicin + cytarabine                                | 46          | I     | Completed               | NCT00840346    |
| Diffuse large B-cell lymphoma (DLBCL)                                     | Panobinostat + rituximab                                              | 42          | II    | N/A                     | NCT01238692    |
| Relapsed and refractory lymphoma                                          | Panobinostat + everolimus                                             | 31          | I/II  | Completed               | NCT00967044    |
| Gliomas                                                                   | Panobinostat + everolimus                                             | 32          | II    | Recruiting              | NCT03632317    |
| Recurrent multiple myeloma, Non-Hodgkin lymphoma, or Hodgkin lymphoma     | Panobinostat + everolimus                                             | 124         | I/II  | Active, not recruiting  | NCT00918333    |
| Relapsed/refractory peripheral T-cell lymphoma or NK/T-cell lymphoma      | Panobinostat + bortezomib                                             | 25          | II    | Completed               | NCT00901147    |
| Relapsed or relapsed- and refractory multiple myeloma                    | Panobinostat + bortezomib                                            | 240         | II    | Recruiting              | NCT02654990    |
| Relapsed multiple myeloma                                                | Panobinostat + bortezomib + dexamethasone                             | 768         | III   | Completed               | NCT01023308    |
| Relapsed or refractory Hodgkin lymphoma                                   | Panobinostat + lenalidomide                                           | 24          | II    | Completed               | NCT01460940    |
| **Mocetinostat (MGCD0103)-based trials**                                 |                                                                        |             |       |                         |                |
| Advanced solid tumors or non-Hodgkin lymphoma                            | Mocetinostat                                                           | 42          | I     | Completed               | NCT00323934    |
| Refractory chronic lymphocytic leukemia                                  | Mocetinostat                                                           | 21          | II    | Completed               | NCT00431873    |
| Relapsed and refractory lymphoma                                          | Mocetinostat                                                           | 74          | II    | Completed               | NCT00359086    |
| Tumors                                                                    | Mocetinostat + gemcitabine                                            | 47          | I/II  | Completed               | NCT00372437    |
| Relapsed or refractory Hodgkin lymphoma                                   | Mocetinostat + brentuximab vedotin                                    | 7           | I/II  | Active, not recruiting  | NCT02429375    |
| Advanced solid tumors and NSCLC                                           | Mocetinostat + durvalumab                                             | 119         | I/II  | Active, not recruiting  | NCT02805660    |
| Metastatic leiomyosarcoma                                                 | Mocetinostat + gemcitabine                                            | 20          | II    | Completed               | NCT02303262    |
| Non-small-cell lung cancer                                               | Mocetinostat + glesatinib + sitravatinib + nivolumab                 | 209         | II    | Recruiting              | NCT02954991    |
| Condition Design Sample size Phase Current status NCT |
|-----------------------------------------------------|-------------|-------|-----------------|----------|
| Advanced myeloma CI-994 6 II Completed NCT00005624 |
| Advanced pancreatic cancer CI-994 + gemcitabine N/A II Completed NCT00004861 |
| Advanced non-small-cell lung cancer CI-994 + gemcitabine N/A III Completed NCT0005093 |
| Recurrent high-grade gliomas Romidepsin 50 I/II Completed NCT0085540 |
| Progressive or relapsed peripheral T-cell lymphoma Romidepsin 131 II Active, not recruiting NCT00426764 |
| Soft tissue sarcoma Romidepsin 40 II Completed NCT00112463 |
| Squamous cell carcinoma of the head and neck Romidepsin 14 II Completed NCT00084682 |
| Metastatic breast cancer Romidepsin 37 II Completed NCT00098397 |
| Relapsed small-cell lung cancer Romidepsin 36 II Completed NCT00086827 |
| Recurrent primary brain tumors Suramin N/A II Completed NCT00002639 |
| Hormone-refractory prostate cancer Suramin 390 III Completed NCT00002723 |
| Metastatic renal cell (kidney) cancer Suramin + fluorouracil 36 I/II Completed NCT00083109 |
| Advanced non-small-cell lung cancer Suramin + docetaxel 80 II N/A NCT01671332 |
| Stage III/IV breast cancer Suramin + paclitaxel 31 I/II Completed NCT00054028 |
| Stage III or IV non-small-cell lung cancer Suramin + paclitaxel + carboplatin 82 II Completed NCT00069292 |
| Poor-prognosis prostate carcinoma Suramin + flutamide + leuprolide 70 II Completed NCT00001266 |
| Prostate cancer Suramin + flutamide + hydrocortisone N/A III Completed NCT00002881 |
| Relapsed or refractory AML Romidepsin 47 II Completed NCT0062075 |
| Relapsed or refractory multiple myeloma Romidepsin 50 II Completed NCT00666388 |
| Relapsed or refractory non-Hodgkin lymphoma Romidepsin 35 II Completed NCT00771914 |
| Triple-negative breast cancer (TNBC) Romidepsin + nivolumab + cisplatin 54 I/II Recruiting NCT02393794 |
| Relapsed/refractory T-cell lymphoma Romidepsin + tenalisib 42 I/II Recruiting NCT01947140 |
| Peripheral T-cell lymphoma (PTCL) Romidepsin + ixazomib 48 I/II Recruiting NCT03547700 |
| Relapsed/refractory lymphoid malignancies Romidepsin + pralatrexate 93 II Recruiting NCT01947110 |
| Relapsed or refractory lymphomas and myeloma Romidepsin + lenalidomide 62 II Active, not recruiting NCT01755975 |
| Relapsed or refractory B- and T-cell lymphomas Romidepsin + lenalidomide + carfilzomib 31 I/II Active, not recruiting NCT02341014 |
| Peripheral T-cell lymphoma Romidepsin + lenalidomide 35 II Recruiting NCT02232516 |
| Skin cancer prevention Nicotinamide 120 II Recruiting NCT03769285 |
| Lung cancer Nicotinamide 110 II/III Active, not recruiting NCT02416739 |
| Bladder cancer Nicotinamide + radiation + carbogen 330 III Completed NCT00033436 |

**Inhibitors of sirtuins**

**Suramin-based trials**

| Condition Design Sample size Phase Current status NCT |
|-----------------------------------------------------|-------------|-------|-----------------|----------|
| Recurrent primary brain tumors Suramin N/A II Completed NCT00002639 |
| Hormone-refractory prostate cancer Suramin 390 III Completed NCT00002723 |
| Metastatic renal cell (kidney) cancer Suramin + fluorouracil 36 I/II Completed NCT00083109 |
| Advanced non-small-cell lung cancer Suramin + docetaxel 80 II N/A NCT01671332 |
| Stage III/IV breast cancer Suramin + paclitaxel 31 I/II Completed NCT00054028 |
| Stage III or IV non-small-cell lung cancer Suramin + paclitaxel + carboplatin 82 II Completed NCT00069292 |
| Poor-prognosis prostate carcinoma Suramin + flutamide + leuprolide 70 II Completed NCT00001266 |
| Prostate cancer Suramin + flutamide + hydrocortisone N/A III Completed NCT00002881 |

**Inhibitors for HATs**

**CBP-targeted therapy**

| Condition Design Sample size Phase Current status NCT |
|-----------------------------------------------------|-------------|-------|-----------------|----------|
| Advanced myeloid malignancies PRI-724 49 I/II Completed NCT01606579 |
| Advanced pancreatic adenocarcinoma PRI-724 + gemcitabine 20 I Completed NCT01764477 |

**BRD (BET) inhibitors**

**GSK525762 (I-BET762, molbresib)-based trials**

| Condition Design Sample size Phase Current status NCT |
|-----------------------------------------------------|-------------|-------|-----------------|----------|
| Relapsed, refractory hematologic malignancies GSK525762 180 I Recruiting NCT01943851 |
| NUT midline carcinoma (NMC) and other cancers GSK525762 195 I Active, not recruiting NCT01587703 |
| Castration-resistant prostate cancer GSK525762 + androgen deprivation therapy 37 I Active, not recruiting NCT03150056 |
| Advanced or metastatic breast cancer GSK525762 + fulvestrant 294 II Recruiting NCT02964507 |

**CPI-0610-based trials**

| Condition Design Sample size Phase Current status NCT |
|-----------------------------------------------------|-------------|-------|-----------------|----------|
| Multiple myeloma CPI-0610 30 I Completed NCT02157636 |
| Progressive lymphoma CPI-0610 64 I Active, not recruiting NCT01949883 |

**RO6870810 (TEN-010, RG6146, JQ2)-based trials**

| Condition Design Sample size Phase Current status NCT |
|-----------------------------------------------------|-------------|-------|-----------------|----------|
| AML, MDS RO6870810 26 I Completed NCT02308761 |
| Advanced solid tumors RO6870810 52 I Completed NCT01987362 |
(HPCs), whereas second-generation HPCs, such as oxamflatin, SAHA, suberic bishydroxamic acid (SBHA), and m-carbocyclic sodium bishydroxamate (CBHA), have shown better inhibition of HDACs and anticancer effects than first-generation agents. Benzamide inhibitors (MS-275, MGCD0103, and CI-994) are well-studied and show promising effects in the treatment of diseases, especially cancers. They inhibit histone deacetylation via binding to catalytic zinc ions within HDACs through carbonyl and amino groups. Inhibition of HDACs by benzamide inhibitors is thought to be reversible, but the bond may become tight and pseudoirreversible in a time-dependent manner. However, benzamide inhibitors have less activity than members of the hydroxamate or cyclic peptide families, with an effective concentration around the micromolar range. Cyclic peptides can be further divided into two groups: cyclic tetrapeptide containing a 2-amino-8-oxo-9, 10-epoxy-decanoyl (AOE) moiety (HC-toxin, trapoxin) and cyclic peptides without the AOE moiety (apicidin and romidepsin). The epoxketone group is essential for the inhibitors to bind to active zinc ions, but the epoxketone-based bond is irreversible. Trapoxin is a fungal cyclic peptide and can irreversibly inhibit the activity of HDACs. Romidepsin, also known as FK228, most likely relies on one of the thiol groups to coordinate to the active site zinc ion. Garlic-associated derivatives, such as diallylsulfide and allylmercaptan, are capable of generating a thiol group that makes them potential inhibitors of HDACs. K-trap, an analog of trapoxin, and other derivatives, including 9-acyloxyapicidins and 9-hydroxyapicidins, have been under investigation. Depudecin is a natural epoxide fungal cyclic peptide containing a 2-amino-8-oxo-9, 10-epoxy-decanoyl (AOE) moiety (HC-toxin, trapoxin) and cyclic peptides without the AOE moiety (apicidin and romidepsin). The epoxketone group is essential for the inhibitors to bind to active zinc ions, but the epoxketone-based bond is irreversible. Trapoxin is a fungal cyclic peptide and can irreversibly inhibit the activity of HDACs. Romidepsin, also known as FK228, most likely relies on one of the thiol groups to coordinate to the active site zinc ion. Garlic-associated derivatives, such as diallylsulfide and allylmercaptan, are capable of generating a thiol group that makes them potential inhibitors of HDACs. K-trap, an analog of trapoxin, and other derivatives, including 9-acyloxyapicidins and 9-hydroxyapicidins, have been under investigation. Depudecin is a natural epoxide derivative isolated from the fungus Alternaria brassicicola. Psammaplins is isolated from a marine sponge Pseudoceratina purpurea. These two natural extracts can inhibit the activity of HDACs. Early HDAC inhibitors were nonselective because of the high homology of the structure and catalytic mechanism of HDACs within each group. The first selective HDAC inhibitor was tubacin, which targets HDAC6 with increased tubulin acetylation but not histone acetylation. PCI-34051, a specific inhibitor of HDAC8, can induce caspase-dependent apoptosis in T-cell lymphoma but does not increase histone acetylation. Another benzamide inhibitor, SHI-1-2, shows HDAC1/HDAC2-specific inhibitory activity that is >100-fold more selective than that of other HDACs. New synthetic chemicals, such as SK7041 and spletomicin, selectively target class I HDACs and sir2-like family members, respectively. The same efforts have been made to develop inhibitors for sirtuins, the class III HDACs. Nicotinamide, a byproduct of the sirtuin enzyme reaction, is a widely used inhibitor of all sirtuins. Other compounds, such as caminol, salermide, tenovin, EX-527, suramin, and AGK2, have also been reported as sirtuin inhibitors. Sirtuin inhibitors (such as nicotinamide) function via interactions with the NAD+ within the active site of sirtuins or through binding to acetyl-lysine.

Of note, second-generation HDACs, including hydroxamic acids (vorinostat (SAHA), belinostat (PXD101), LAQ824, and panobinostat (LBH589)) and benzamides (entinostat (MI-275), tacedinaline (CI-994), and mocetinostat (MGCD0103)), are currently in clinical trials, and some of them have already been approved for disease treatment. The success of romidepsin in phase I clinical trials in cutaneous and peripheral T-cell lymphoma accelerated the development of HDAC inhibitors as anticancer drugs. In 2004, SAHA (vorinostat) was first approved by the US Food and Drug Administration (FDA) for the treatment of cancer, restricted to patients with cutaneous T-cell lymphoma (CTCL), as an HDAC inhibitor. Romidepsin (Istodax) was the second approved HDAC inhibitor, which was approved in 2009. Three members of the benzamide family have also shown clinical significance in anticancer drug development. Belinostat (Beleodaq, previously known as PXD101) was approved in 2014 by the US FDA and European Medicines Agency to treat peripheral T-cell lymphoma. Another HDAC inhibitor, panobinostat, is a nonselective HDAC (pan-HDAC). It has shown promising effects in anticancer treatments; therefore, the FDA accelerated its approval for the treatment of patients with multiple myeloma. Intriguing, as we mentioned before, truncating mutations in HDAC2 have been found in sporadic carcinomas and colorectal cancer and result in resistance to traditional HDAC inhibitors. Mutations in other HDACs also exist; therefore, screening of these mutations in cancer can improve the efficacy of HDAC inhibitors.

### Table 6 continued

| Condition                        | Design                  | Sample size | Phase | Current status | NCT          |
|----------------------------------|-------------------------|-------------|-------|----------------|--------------|
| Advanced multiple myeloma        | RO6870810               | 86          | I     | Recruiting     | NCT03068351 |
| Advanced ovarian cancer or triple-negative breast cancer | RO6870810 + atezolizumab | 116         | I     | Suspended      | NCT03292172 |
| High-grade B-cell lymphoma       | RO6870810 + venetoclax + rituximab | 94          | I     | Recruiting     | NCT03255096 |
| BAY1238097-based trials          | BAY1238097              | 8           | I     | Terminated     | NCT02369029 |
| Neoplasms                        |                         |             |       |                |              |
| MK8628 (OTX-015, biraibresib)-based trials |                     |             |       |                |              |
| Advanced solid tumors            | MK-8628                 | 47          | I     | Completed      | NCT02259114 |
| Hematologic malignancies         | MK-8628                 | 9           | I     | Active, not recruiting | NCT02698189 |
| Hematologic malignancies         | MK-8628                 | 141         | I     | Completed      | NCT01713582 |
| FT-1101-based trials             | FT-1101                 | 160         | I     | Recruiting     | NCT02543879 |
| Relapsed or refractory hematologic malignancies |                     |             |       |                |              |
| INC8057643-based trials          | INC8057643              | 136         | I/I   | Active, not recruiting | NCT02711137 |

Lenalidomide, derivative of thalidomide; duvralumab, anti-PD-L1 monoclonal antibody; avelumab, anti-PD-L1 monoclonal antibody; bevacizumab, VEGF inhibitor; temsirolimus, mTOR inhibitor; rituximab, anti-CD20 monoclonal antibody; regorafenib, multikinase inhibitor; nivolumab, anti-PD-1 monoclonal antibody; panobinostat, nonselective HDAC (pan-HDAC).
replacing the ribose moiety. EPZ-5767 also shows synergistic effects with cytarabine, daunorubicin, and the DNMT inhibitor azacitidine in treatments for ALL with MLL translocation. EPZ-5767, though still showing low oral bioavailability, has been investigated in clinical trials for the treatment of leukemia with MLL rearrangement. There are several inhibitors of EZH2. 3-Deazaneplanocin A (DZNep), a derivative of the antibiotic neplanocin-A, is one of the most studied compounds. In fact, DZNep is a SAH-hydrolase inhibitor and decreases EZH2 expression via upregulation of SAH, which leads to degradation of PRC2 in a feedback inhibition mechanism. Another kind of inhibitor is SAM competitive inhibitors. EI1, a small molecular inhibitor of EZH2, inhibits EZH2 activity by directly binding to EZH2 and competing with SAM. GSK005687, a potent inhibitor of EZH2, significantly reduces H3K27 methylation in lymphoma cells with point mutations at the Tyr641 and Ala677 residues of EZH2 without obvious effects on the proliferation of wild-type cells. EPZ-6438, which shows similar effects and superior oral bioavailability, was developed next. CPI-1205 is a novel inhibitor of EZH2 that belongs to the pyridone family.

Tranylcypromine (TCP) is an approved drug for depression due to its ability to inhibit monoamine oxidase (MAO) activity. The structures of LSD enzymes and MAOs share many similarities. Therefore, the side effects of TCP as an HDMT inhibitor, including orthostatic hypotension, dizziness, and drowsiness, are mostly caused by targeting of MAO. Administration of TCP in MLL-AF9 leukemia promotes tumor cell differentiation and apoptosis.
The treatment of cancer patients. Daminozide (N-(dimethylamino) succinamic acid, 160 Da), a plant growth regulator, selectively inhibits KDM2/7 by chelating the active site metal.662 Daminozide and siRNA can similarly downregulate KDM7 expression and then regulate tumor-repopulating cells via demethylation of H3K9.663

Table 8. Important ongoing clinical trials with combination therapies including DNA methylation and histone modification.

| Condition | Design | Sample size | Phase | Current status | NCT    |
|-----------|--------|-------------|-------|---------------|--------|
| Histone acetylation inhibitor + DNA methylation inhibitor | Azacitidine + pracinostat | 85 | I | Completed | NCT00741234 |
| MDS | Azacitidine + pracinostat | 102 | II | Completed | NCT01873703 |
| High-risk MDS | Azacitidine + pracinostat | 60 | II | Active, not recruiting | NCT03151304 |
| AML | Azacitidine + pracinostat | 500 | III | Recruiting | NCT03151408 |
| MDS | Azacitidine + mocetinostat | 18 | I/II | Completed | NCT02018926 |
| High-risk MDS, AML | Azacitidine + mocetinostat | 66 | I/II | Completed | NCT00324220 |
| Advanced cancers | Azacitidine + valproic acid | 69 | I | Completed | NCT00496444 |
| AML, MDS | Azacitidine + valproic acid | 50 | II | Recruiting | NCT02124174 |
| Intermediate II and high-risk MDS | Azacitidine + valproic acid | 62 | II | Completed | NCT00496737 |
| AML, MDS | Azacitidine + valproic acid + ATRA | 34 | II | Completed | NCT00326170 |
| High-risk MDS | Azacitidine + valproic acid/fenaldimide/idarubicin | 320 | II | Active, not recruiting | NCT01342692 |
| Higher-risk MDS, CML | Azacitidine + vorinostat | 282 | II | Active, not recruiting | NCT01522976 |
| AML, high-risk MDS | Azacitidine + vorinostat | 260 | II | Active, not recruiting | NCT01617226 |
| AML, MDS | Azacitidine + vorinostat | 135 | I/II | Active, not recruiting | NCT00392353 |
| Relapsed/refractory lymphoma | Azacitidine + vorinostat | 17 | I/II | Completed | NCT01120834 |
| Relapsed/refractory lymphoid malignancies | Azacitidine + romidepsin | 60 | I/II | Recruiting | NCT01998035 |
| Relapsed or refractory AITL | Azacitidine + romidepsin + bendamustine + gencitabine | 86 | III | Recruiting | NCT03930018 |
| Lymphoma | Azacitidine + romidepsin + durvalumab + pralatrexate | 148 | I/II | Recruiting | NCT03161223 |
| Advanced non-small-cell lung cancer | Azacitidine + entinostat | 162 | II | Completed | NCT00387465 |
| AML | Azacitidine + entinostat | 108 | II | Recruiting | NCT01305499 |
| Advanced breast cancer | Azacitidine + entinostat | 58 | II | Active, not recruiting | NCT01349959 |
| AML, MDS, CML | Azacitidine + entinostat | 197 | II | Completed | NCT00313586 |
| Metastatic colorectal cancer | Azacitidine + entinostat | 47 | II | Completed | NCT01105377 |
| Non-small-cell lung cancer | Azacitidine + entinostat + nivolumab | 120 | II | Recruiting | NCT01928576 |
| Leukemia, lung cancer, lymphoma, multiple myeloma, prostate cancer | Azacitidine + phenylbutyrate | N/A | II | Completed | NCT00006019 |
| AML with 11q23 rearrangement | Azacitidine + pinomostat | 36 | I/II | Not recruiting | NCT03701295 |
| High-risk MDS | Azacitidine + GSK2879552 | 74 | I/II | Recruiting | NCT02929498 |
| AML, MDS | Decitabine + valproic acid | 153 | II | Completed | NCT00414310 |
| Relapsed/refractory MDS, leukemia | Decitabine + valproic acid | 54 | I/II | Completed | NCT00075010 |
| AML | Decitabine + valproic acid | 204 | II | Completed | NCT00867672 |
| AML, MDS | Decitabine + vorinostat | 71 | I | Completed | NCT00479232 |
| AML, MDS | Decitabine + panobinostat | 52 | I/II | Recruiting | NCT00691938 |
| Relapsed or refractory leukemia and MDS | Decitabine + romidepsin | 36 | I | Completed | NCT00114257 |
| Advanced lung cancer | Guadecitabine + mocetinostat + pembrolizumab | 40 | I | Recruiting | NCT03220477 |
| Lung cancer | Hydralazine + valproic acid | 29 | I | Recruiting | NCT00996060 |
| Metastatic cervical cancer | Hydralazine + valproate | 143 | III | N/A | NCT00532818 |
| Ovarian cancer | Hydralazine + valproate | 211 | III | N/A | NCT00532999 |
| Cervical cancer | Hydralazine + valproate + cisplatin chemoradiation | 18 | II | Completed | NCT00404326 |
| Refractory solid tumors | Hydralazine + magnesium valproate | 15 | II | Completed | NCT00405058 |
| BET inhibitor + DNA methylation inhibitor | FT-1101 + azacitidine | 160 | I | Recruiting | NCT02543879 |
| Relapsed or refractory hematologic malignancies | GSK3326595 (selective inhibitor of protein arginine methyltransferase 5 (PRMT5)) vs azacitidine | 302 | I/II | Recruiting | NCT03614728 |

Pembrolizumab, anti-PD-1 monoclonal antibody; lenalidomide, derivative of thalidomide; durvalumab, anti-PD-L1 monoclonal antibody; nivolumab, anti-PD-1 monoclonal antibody.
103182, a selective inhibitor of KDM5B, has shown promising results in terms of antiproliferative effects in hematological and solid cancer cells. KDM8 and JMJD6 share homology and can be inhibited by a broad spectrum inhibitor, NOG.661 solid cancer cells. KDM8 and JMJD6 share homology and can be inhibited by a broad spectrum inhibitor, NOG.661. 103182, a selective inhibitor of KDM5B, has shown promising effects that can inhibit HDAC1/2/3 and LSD1 with similar low micromolar potency. This drug is under clinical investigation. Other studies have administered two or more kinds of epigenetic drugs for anticancer therapy. Relevant clinical trials are listed in Table 8.

CONCLUSION
Although more specific mechanisms need to be investigated, it is well accepted that epigenetic events are important in normal biological processes as well as in tumorigenesis and that the epigenetic status is usually widely altered during cancer initiation. This makes epigenome-targeted therapy a promising strategy for the treatment of cancer. Based on the complexity of cancer, epigenetic alterations have influenced multiple aspects in cancer, such as the expression of oncogenes and tumor suppressor genes and signal transduction, resulting in enhanced cancer growth, invasion and metastasis. Although epigenetic therapy has a rational and profound basis in theory, some problems remain to be discussed and solved. The first and most important is the problem of selectivity. Epigenetic events are ubiquitously distributed across normal and cancer cells. In fact, some cancers depend on certain epigenetic alterations and can be sensitive to this regulation, whereas under usual regulation, normal cells have the ability to compensate for these epigenetic changes. Therefore, the priority is to determine the most important epigenetic alterations for different cancers. The second problem extends from the first problem. Thus far, epigenetic therapy has obtained impressive results in hematological malignancies but not in solid tumors. The properties of hematological malignant cells and solid tumor cells are different. However, researchers have still investigated the appropriate strategies for solid tumors. Since epigenetic alterations have effects on the sensitivity of small molecule targeted therapy and chemotherapy or radiotherapy, epigenetic-targeted therapy seems to be an important adjunctive therapy. The combination of epigenetic therapy and immunotherapy has also been investigated in preclinical and clinical trials. Based on the achievements obtained, epigenetic-targeted therapy is a promising strategy for anticancer treatment. Epigenomes in cancer are related to many aspects during cancer initiation. A better understanding of the specific mechanisms underlying those alterations in different cancers is necessary. Meanwhile, optimized treatment options, including a variety of combinations, still remain to be discovered.

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ADDITIONAL INFORMATION
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