Review Article

Su Bu, Ting Ye, Hang Gao, Hang Song* and Yongfu Zhu*

Histone methylation and acetylation in cancer: mechanism, progression, and targets

https://doi.org/10.1515/oncologie-2024-0324
Received June 27, 2024; accepted August 15, 2024;
published online September 20, 2024

Abstract: Along with the continuous development of chromatin immunoprecipitation sequencing and its derivative technologies, as well as an increased understanding of epigenetic modification, the post-translational modification of histones has gradually been revealed, including their acetylation, methylation, phosphorylation, and ubiquitination, and their roles in diseases, especially cancer, have also been gradually explored. The role and regulation of histone methylation and acetylation in cancer and the mechanism of action of drugs have been thoroughly discussed. In particular, the review highlights recent advances in the development of epigenetic-targeted therapies and the challenges that remain in translating these findings into clinical applications. Research on epigenetic-targeted drugs is in its infancy, and more research in the fields of dominant biology, structural biology, and pharmacodynamics is needed. Through this review, the authors aim to provide theoretical guidance for the construction and clinical transformation of histone methylation and acetylation.

Keywords: histone; epigenetic modification; methylation; acetylation; targeted drugs

Introduction

Histones are composed of nucleosome-modulated chromatin remodeling and regulate gene expression [1]. The post-translational modification (PTM) of histone includes methylation, acetylation, ubiquitination, and phosphorylation [2]. The type of histone modifications can be regarded as a “histone code” [3]. The N-acetylation of lysine is a typical histone modification. Generally, the acetylation of histone lysine affects transcriptional activation [4]. And different methylated sites lead to different results. Histones are organized in a manner in which double-stranded DNA is wrapped around the center of a protein made up of proteins. Multiple hydrogen bonds allow DNA to bind to protein centers formed by histones in each nucleosome. In most cases, these bonds form between the amino acid backbone of the histone and the sugar-phosphate backbone of the DNA. Some hydrophobic interactions and ionic bonds are also involved. For instance, methylation of lysine K4 on H3 affects transcriptional activation [5]. The methylation of K9 or K27 on H3, as well as the methylation of K20 on H4, are both linked to transcriptional repression [2]. Additionally, Lysine contains many methylation states, including mono-, di-, or tri-methylated states. Gene expression is mainly regulated by the methylation states of Lysine. For instance, compared with the monomethylation of histone H3 lysine 9 (H3K9) at active genes, its trimethylation is usually observed at repression genes [6].

Numerous studies have demonstrated that the compounds that target the methylation and acetylation of histone represent a novel class of anti-tumor drugs. For instance, Vorinostat and Romidepsin, both histone deacetylase inhibitors (HDACis), can be used to treat cutaneous T cell lymphoma, and have been officially approved by the U.S. Food and Drug Administration (FDA) [7]. This review explores the association between histone modification and cancer development, focusing on methylation and acetylation, and discusses the potential efficacy of these modifications in cancer treatment.

Histone and epigenetic modification

DNA is packaged into nucleosomes to form chromatin or chromosomes and thus acts as a barrier for transcription [1]. Nucleosomes are composed of histones, including H2A, H2B,

Su Bu and Ting Ye contributed equally to this work.

***Corresponding authors: Hang Song**, School of Integrated Chinese and Western Medicine, Anhui University of Chinese Medicine, Hefei, China, E-mail: hangsong@ahtcm.edu.cn; and **Yongfu Zhu**, The First Department of Oncology, The First Affiliated Hospital of Anhui University of Chinese Medicine, Hefei, China, E-mail: zyf240@ahtcm.edu.cn
Su Bu, Clinical Laboratory Center, The First Affiliated Hospital of Anhui University of Chinese Medicine, Hefei, China
Ting Ye and Hang Gao, Graduate School, Anhui University of Chinese Medicine, Hefei, China

H3, H4, and H1. These histones can be modified by acetylation, methylation, ubiquitination, and phosphorylation [8], all of which are epigenetic modifications. The term "epigenetics" indicates a heritable alteration in gene expression by modifications, but not through a concomitant change in the primary DNA sequence. In addition to histone modifications, there are two other typical types of histone modification, including DNA methylation and RNA interference which play important roles in the regulation of gene expression and nuclear architecture.

Histone modifications play a key role in cell differentiation and organismal development [9]. It has been reported that at least 11 types of modifications can be found in over 60 different amino acid residues on histones, including (but not limited to) methylation, acetylation, formylation, sumoylation, proline isomerization, propionylation, and phosphorylation. In the nucleus of eukaryotic cells, DNA is packaged into highly tissue-rich chromatin structures. The building blocks of chromatin are known as nucleosomes and consist of 147 pairs of bases to DNA wrapped around an octameric protein complex that involves two copies of each of the four histones: H3, H4, H2A, and H2B. Histones are subject to various modifications through the addition of chemical groups to their globular domains and to the N-terminal tail protruding from the nucleic core particles. In addition, histones are predominant in their unstructured tails and are decorated with many post-translational modifications (PTM) or co-translational modifications (CTM) translational modifications on their globular domains [10]. Two major mechanisms are involved in chromatin-templated processes [11]. Firstly, histone modifications can regulate chromatin structure and access transcription factors by changing the net charge of the histone molecules or inter-nucleosomal interactions. Secondly, histone modifications can recruit protein PTM-specific binding proteins, and recognize modified histones *via* chromo-, bromo- and plant homeodomain (PHD) domains [12] (Figure 1).

Generally, it is thought that the PTMs of histones are located in the N-terminal tail domain of core histones. However, novel PTM sites are being continuously discovered and the globular domain of core histones is of great importance for histone-DNA and histone-histone interactions [12]. A study on the O-linked N-acetylglucosamine (O-GlcNAc) modification of histones has demonstrated that additional PTM sites can be discovered [13].

Methylation and acetylation of histone in cancer progression

Numerous studies have verified that epigenetics plays an important role in carcinogenesis. Apart from global changes in histone modifications, the epigenome can be altered during tumorigenesis [14]. The methylation and acetylation of histones have been shown to be closely associated with tumorigenesis and progression [13]. For instance, as a common type of cancer, colon cancer has shown a potential relationship with higher histone methylation activity [15].

Histone methylation and demethylation

Generally, H3K4, H3K36, H3K27, and H4K20 [16] are regarded as the best-characterized sites of histone methylation and are often located on lysine residues. In histone H3 and H4 lysine methylation, several arginine residues have been found to be overexpressed in tumors. Mutations in H3K4 methyltransferases significantly increase susceptibility to various cancers [17]. There are different methylation states, such as the most common types: mono-(me), di-(me2), and tri-(me3). They are also located in different genomic regions. For example, H3K4me1 is modified at active enhancers and H3K4me2/3 often spans the transcriptional start site of

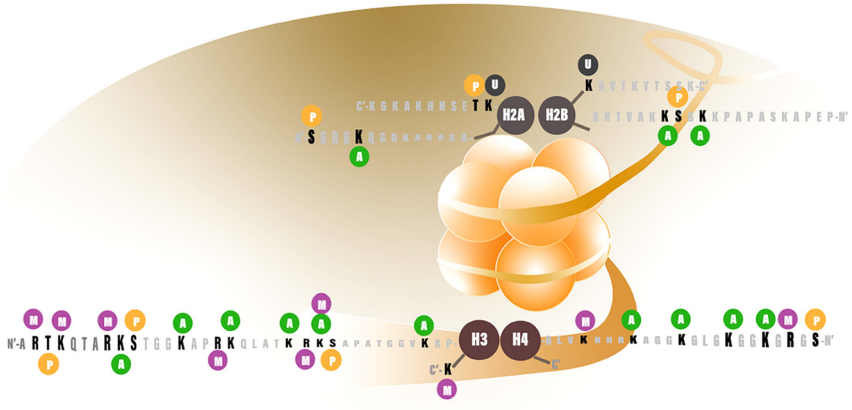

Figure 1: Modifications and amino acid residues on histones.

activated genes [18]. In addition, H3K9me can be observed at active genes, but tri-H3K9me is usually located in gene repression.

In recent years, studies have shown that histone methylation plays a key role in a variety of pathophysiological processes. Histone methylation can both promote and inhibit gene expression depending on the methylation site. H3K4me3 is generally associated with gene activation, while H3K27me3 is associated with gene silencing [19]. The role of these modifications in cancer, neurodegenerative diseases, and inflammatory diseases has been extensively studied. For example, aberrant expression of H3K27me3 has been implicated in the occurrence and progression of a variety of cancers. By understanding the mechanisms of these epigenetic modifications, we can develop novel therapeutic strategies to modulate aberrant gene expression patterns and improve pathophysiological states.

Histone methylation can regulate the transcriptional and post-transcriptional levels of certain core genes of tumorigenesis and immune response. For instance, low enrichment of repressive histones in the promoter regions (H3K27me3 and H3K9me3) may be associated with programmed death receptor 1 (PD-1), Lymphocyte activation gene 3 (LAG-3), cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) gene expression in breast cancer [20]. In addition, the low abundance of H3K9me3 and H3K27me3 in the promoter region of TIM-3 and TIGIT may be associated with the upregulation of these genes in breast and colorectal cancer, respectively [21] (Figure 2). H3K9me3 is typically associated with heterochromatin and involves the recruitment of heterochromatin protein 1 (HP1), maintaining gene silencing, especially in genomic silencing regions and centromeres. H3K27me3 is mainly regulated by the polycomb repressive complex 2 (PRC2), which binds to and modifies specific gene promoters to suppress the expression of developmental and differentiation-related genes [19]. When these repressive marks are reduced in gene promoter regions, transcription factors and other activators can more easily bind to DNA, leading to gene transcription activation. This depressive effect can reduce immune inhibitory signals, promote immune evasion by tumor cells, and accelerate tumor growth and metastasis [22].

Histone acetylation and deacetylation

As a highly reversible process, histone acetylation is regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs) [23]. HATs catalyze the lysine residues of histone acetylated at the N-terminus and lead to transcription activation [24, 25]. Deacetylation of histone is catalyzed by HDACs, which leads to the alteration of the structure of chromatin, which may dictate the accessibility of DNA to its corresponding transcription factors and co-activators.

It has been reported that the imbalance in histone acetylation or deacetylation is an important characteristic of tumorigenesis and development [26]. Relevant studies have shown that histone acetylation is often associated with gene activation, which promotes gene expression by relaxing chromatin structure and making it easier for transcription factors to bind to DNA. Aberrant regulation of histone acetylation levels is thought to be a key factor in pathophysiological processes in a variety of diseases [27]. For example, the aberrant activity of HDACs is strongly associated with the development of cancer, HDACs can limit accessibility between a transcription factor and their binding site, as well as induce the confirmation ability of closed chromatin, which leads to the inhibition of the transcription of tumor suppression and immune response genes [28, 29] (Figure 3). In addition, the role of acetylation in neurodegenerative diseases has received increasing attention, and studies have found that alterations in histone acetylation may affect neuronal survival and function [30].

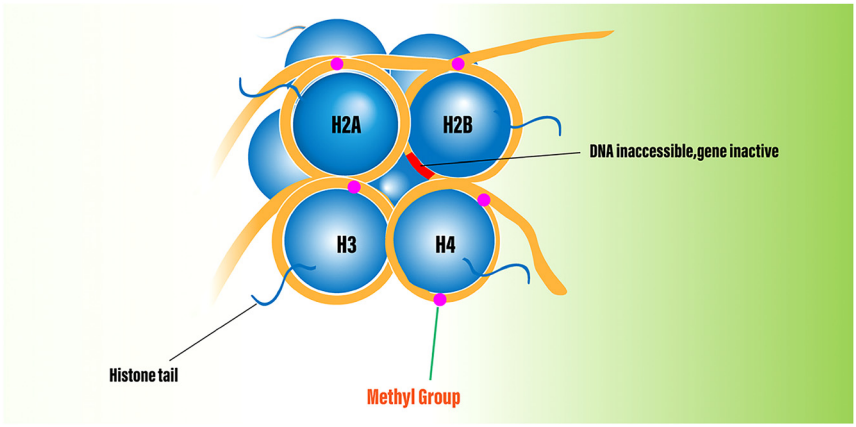

Figure 2: Histone methylation and demethylation.

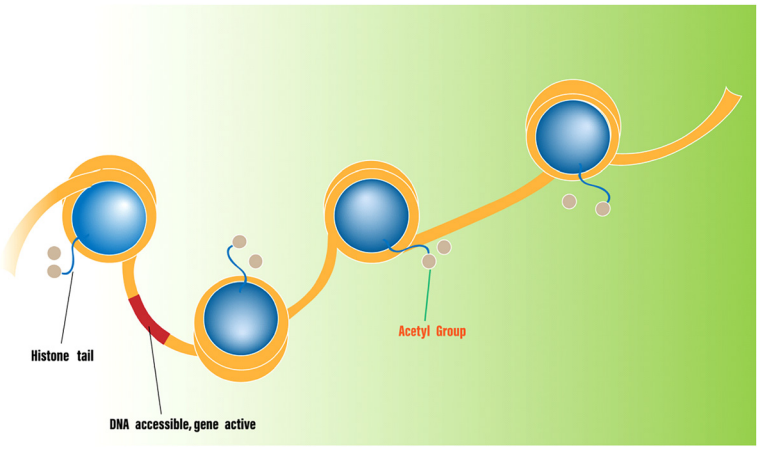

Figure 3: Histone acetylation and deacetylation in cancer.

These findings further underscore the importance of histone acetylation in maintaining the normal function and health of cells.

The influencing mechanism of histone methylation and acetylation on cancer progression

Histone modifications act as signals for transcription factors and chromatin remodelers and can drive distinct downstream functions between histone-histone or histone-DNA interactions [31]. The misregulation of histone modifications is often associated with cancer [32]. Methylation and acetylation are the most common among the different known types of histone modification.

Histone methylation

At present, cancer research has suggested that the physiological and pathological functions of methylation focus on gene regulation, DNA recombination, and damage repair, as well as cell differentiation [33]. For instance, the disruptor of telomeric silencing 1 like DOT1L has been proven to initiate or maintain an active transcription state, involving many transcription proteins, including AF4/9/10 and ENL [34–37], as H3K79 methyltransferase. A protein complex, which includes AF4, AF9, AF10, and ENL, can recruit DOT1L for methylating H3K79 in acute leukemia, which leads to the overexpression of HoxA9, HoxA7, and Meis1, all of which are leukemia-related genes [38–41]. Isocitrate dehydrogenase (IDH) is another example of a regulator of histone lysine methylation. IDH is a key enzyme tricarboxylic acid cycle [42] that has been demonstrated to show recurrent mutations in various cancers, such as glioma and acute myeloid leukemia (AML) [43, 44]. It has been reported that IDH plays key roles during the early stage of cancers – Mutant IDH proteins acquire neomorphic enzyme activity to produce putative oncometabolite D-2-hydroxyglutarate, which is thought to block cellular differentiation by competitively inhibiting α-ketoglutarate-dependent dioxygenases involved in histone and DNA demethylation [44]. The process of transformation of α-KG to D-2-hydroxyglutaric acid (D2HG) is catalyzed by IDH mutant enzymes [44, 45]. The relatively higher level of D2HG was found to inhibit 5-methylcytosine hydroxylases [46], resulting in genome-wide hypermethylation of histone and DNA [47–49], which blocks cell differentiation [49].

Histone acetylation

Aberrant histone acetylation modifications have been reported to be closely associated with the expression of key genes, including tumor suppressor genes and oncogenes, as well as certain regulatory genes of biology processes, including cell cycle, proliferation, metabolism, apoptosis, and DNA repair [50, 51]. For instance, in acute promyelocytic leukemia, chromosomal translocation leads to the production of fusion proteins. Then, these fusion proteins bind to retinoic acid-responsive elements. This fusion protein has also been reported to be involved in the recruitment process of the HDAC repressor complex [52]. These changes repress the expression of genes associated with the regulation of normal differentiation and proliferation of myeloid cells [53]. Histone acetyltransferase Males absent on the first (MOF) is mainly responsible for the acetylation of histone H4K16. In humans, MOF (hMOF), is a member of the MYST family of HATs. The modulation function of MOF on estrogen receptor α (ERα) action in hepatocellular carcinoma (HCC)

suggests that MOF may be a potential therapeutic target for HCC and that certain pro-apoptotic genes, such as TMS1/ASC, could be regulated by MOF-dependent H4K16ac, which is often silent in human cancers [54].

Histone modification and acetylation regulate cancer and affect progression

Methyltransferases and demethylases regulate histone methylation. Several studies have shown that histone methylation modifications are involved in cancer processes, including methyltransferases, demethylases, and methyl-lysine-binding proteins [55]. The regulation of histone methylation and demethylation can affect cancer progression. For instance, as key genes of the methylation of H3K27, EZH2 has been proven to function as an oncogene in breast and hepatocellular cancer [56, 57]. The overexpression of EZH2 promotes the development of breast and prostate cancer [58], and certain miRNAs control the overexpression of EZH2 in cancer. H3K27 methylation is associated with the inhibition of gene expression [59]. In diffuse large B-cell lymphoma, H3K27me1 can be converted to H3K27me2/3, as the substitution of tyrosine 641 (Y641) within the SET domain of EZH2 through heterozygous missense mutations [60]. It has also been shown that EZH2 mutations are a type of loss-of-function mutation in myeloid malignancies [61, 62]. The PRC2 complex regulates H3K27 methylation through its core subunit, EZH2, and can influence chromatin structure [63]. The combination of DZNep and Panobinostat, a pan-histone deacetylase inhibitor, was shown to be stable and effective for AML, follicular lymphomas, and B-cell lymphomas [64]. In diffused large B-cell lymphoma cells, EI1 can inhibit the enzymatic activity of EZH2 through direct binding to enzymes and competition with methyl donor S-adenosylmethionine, which leads to genome-wide H3K27 methylation loss and the activation of PRC2 target genes and can decrease cell proliferation, and arrest the cell cycle and apoptosis through Y641 mutations [65]. The loss of SMARCB1/INI1 expression of the core subunit of the SWI/SNF complex in epithelioid sarcoma (ES) has a great influence on the occurrence of tumors [66]. SWI/SNF, a chromatin remodeler, exerts an opposite effect to that of PRC2 and has been shown to be associated with tumor inhibition [67, 68]. ES also showed an increase in the expression of EZH2. Tazemetostat functions as an inhibitor of EZH2 to inhibit the methylation of H3K27, thereby inhibiting the expression of ES cells [69]. Tazemetostat has been approved for use in patients with advanced epithelioid sarcoma, with phase 2 trials demonstrating antitumor activity and a high safety profile [70].

There are multiple functional domains in Histone demethylase proteins, including binding, recognizing, catalyzing, and interacting with cofactors. For instance, lysine-specific demethylase 1 (LSD1, KDM1A) can demethylate lysine through an amine oxidation reaction and belongs to the first class of demethylases while flavin adenine dinucleotide (FAD) is a cofactor in this process. Recently, it was reported that LSD1 overexpression is necessary for the occurrence and development of AML [71, 72]. The overexpression of LSD1 has been reported in a variety of cancers [72, 73]. As a specific LSD inhibitor, ORY-1001 can inhibit stem cell colony formation, reduce leukemogenesis, and induce the differentiation of AML [74]. It can modulate the Warburg effect by controlling hexokinase 2 (HK2) expression, thereby significantly inhibiting lung cancer cell proliferation, colony formation, and the cell cycle, and inducing apoptosis [75]. It can also play an important role in breast cancer by blocking CSC-driven breast ball formation in breast cancer cell lines that rely on SOX2 expression [76]. Its effective concentration is in sub-nanomolar scale concentrations and shows a time- and dose-dependent manner while being upregulated in H3K4me2 and causing cellular apoptosis in AML [74].

These findings highlight the crucial role of small molecule inhibitors, such as ORY-1001, in targeting specific histone demethylases. By modulating key pathways and gene expressions, these inhibitors offer promising therapeutic strategies for various cancers.

HATs exert an influence on the epigenetic modulation of gene transcription *via* modifying chromatin histones and can be regulated in cancers and other diseases [23]. HAT1 as an example, has been demonstrated to be associated with upregulated PD-L1 expression in pancreatic cancer [28]. It has been shown that the overexpression of HAT1 can increase the expression of PD-L1 and its knockdown could inhibit the proliferation of pancreatic cancer cells and reduce PD-L1 expression [28]. HAT inhibitors (HATis) can be used as potent blockers of tumorigenesis [77].

HDACis have been well-established as a leading cause of change in the expression of 2–10 % of cellular genes. This can regulate chromatin structure and transcription factors or cofactor binding to promote the acetylation of histones [78]. Vorinostat and Panobinostat are pan-HDACi drugs and have been proven to alter chromatin compaction in the promoter regions of PD-L1 or PD-L2 in TNBC and melanoma [79, 80]. Chromatin compaction can affect the epigenetics of cells, thus becoming a key regulator of silencing genes [81]. HDACis can suppress Tregs and FoxP3 expression, and active

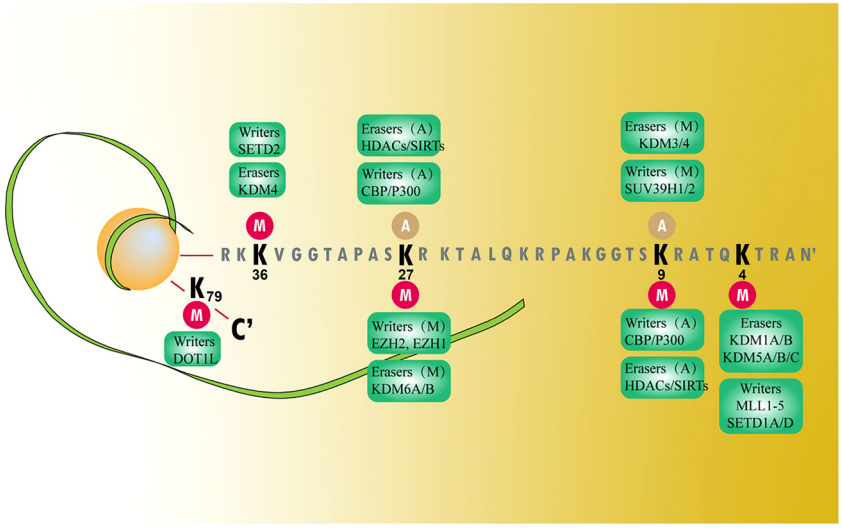

Figure 4: Regulation of histone methylation and acetylation in cancer.

NK cells and its ligands, regulate MHC molecules (class I and II) and CD8+ T cell cytotoxicity (Figure 4).

Anticancer drugs targeting the methylation and acetylation of histones

At present, some drugs based on the methylation and acetylation of histones have been developed for the treatment of cancers (Table 1).

H3K79 methyltransferase (DOT1L)

DOT1L is a key cancer regulator in mixed-lineage leukemia (MLL) rearranged leukemia, and EPZ004777 is its first small molecule inhibitor. Since 2011, numerous studies have reported that EPZ004777 exerts selective anti-cancer activity in MLL. At the same time, other DOT1L inhibitors have been discovered and shown to have a similar effect to that of EPZ004777 [83–86]. Adenosine or analogous structures appear in all DOT1L inhibitors, as strong protein-protein and protein-DNA interactions between DOT1L and substrate nucleosome, showing comparable competitiveness with the enzyme cofactor, S-adenosylmethionine (SAM). Several research reports have shown that EPZ004777, EPZ5676, and SGC0946 can selectively activate an anti-cancer function in MLL-rearranged leukemia cells. Notably, only after two weeks of treatment, these DOT1L inhibitors can exhibit anti-proliferative activities. In MLL-rearranged leukemia cells, EPZ004777 can selectively target the reduction of the expression of MLL oncogenes to impact the apoptosis and differentiation of cells. Moreover, this also prolongs the survival time in an MV4-11 leukemia mouse model. Another

Table 1: Anticancer drugs targeting methylation and acetylation of histone.

Target	Inhibitor drugs	Function	Reference
H3K79 methyltransferase (DOT1L)	EPZ004777 EPZ567 SGC0946	Anti-proliferative activities	[35]
Histone lysine demethylase (LSD1)	Trans-cyclopropylamines	Improving inhibitory activity, increasing LSD1 selectivity	[72]
	GSK2879552	Inhibiting the proliferation ability of cells	[75]
Histone acetyltransferase (HAT)	HAT Tip60 TH1834 Garcinol	Inducing the apoptosis of cells	[25]
Histone deacetylase (HDAC)	Suberoylanilide hydroxamic acid hydroxamic acid CG-1521 Sodium butyrate	Affecting cell mitosis and DNA repairing	[27]
	Entinostat	Enhance the sensitivity of breast cancer to nivolumab and ipilimumab	[82]

potent DOT1L inhibitor, EPZ5676 has been proven to exert an anti-cancer effect *via* the regulation of pharmacokinetics. It can cause low oral bioavailability and relatively high clearance *in vivo*. As a potential drug for the treatment of MLL-rearranged leukemia, EPZ5676 is currently undergoing Phase I clinical trials [87].

LSD1, the inhibitor of histone lysine demethylase

LSD1, a member of the monoamine oxidases (MAO) family, is a histone lysine demethylase [88, 89]. It contains four functional domains, including a SWIRM, an oxidase domain, a putative nuclear localization peptide and a tower domain [90]. In particular, the oxidase domain, the tower domain, and the SWIRM are of great importance for demethylation. The tower domain directly interacts with repressor element-1 silencing transcription factor corepressor 1 to form protein complexes that regulate histone lysine methylation and gene expression. Numerous studies have shown that LSD1 is overexpressed in many types of cancers, including AML, lung, breast, and prostate cancer [91–93]. A variety of small molecule inhibitors of LSD1, belonging to both reversible and irreversible types have been identified [94, 95]. The main feature of irreversible LSD1 inhibitors is that they can permanently deactivate enzymes by binding to flavin adenine dinucleotide (FAD) [96]. Correspondingly, reversible inhibitors of LSD1 cannot covalently bind to any protein.

The first LSD1 inhibitor was derived from Tranylcypromine, which contains a common cyclopropylamine core structure and can be used as an antidepressant drug. Based on the structure of Tranylcypromine, other LSD1 inhibitors have been developed. A second amine-containing N-substituent is a common feature of highly potent LSD1 inhibitors. For example, the cyclopropylamine moiety on the right side, can not only improve the inhibitory activity but can also increase selectivity for LSD1 to MAO-A and -B [97]. GSK2879552, another potent LSD1 inhibitor, has been reported to inhibit the proliferation ability of small cell lung cancer (SCLC) and AML cells. Moreover, it can also play an anti-cancer role in a SCLC mouse model. Mechanistic studies have shown that GSK2879552 can dysregulate the gene expression of TGF-β in SCLC, and its sensitivity to LSD1 inhibition is correlated with DNA hypomethylation, as shown in a gene set of SCLC cells [98].

The inhibitor of histone acetyltransferase (HATi)

As one of the most common modifications of eukaryotic proteins, acetylation can affect a variety of biological processes, including microtubule function, DNA transcription, protein-protein interactions, and peptide-receptor recognition. HATs and HDACs are well-known regulators of the acetylation status of histones. It has been reported that HATi can reduce acetylation levels of histones and exhibit antitumor effects on many cancers [99, 100]. The HATi includes several different structures, such as bisubstrate inhibitors, synthetic compounds, and natural products. In particular, the HAT Tip60 has been identified as a mediator of the response to DNA damage [101]. Its inhibitor, TH1834, can induce the apoptosis of breast cancer cells due to unrepaired DNA damage [102].

The inhibitor of histone deacetylase (HDACi)

HDACs can catalyze deacetylation [103], along with the inhibition of transcriptional processes and the formation of heterochromatin. Currently, HADCs can be divided into four subclasses: class I, class IIa, class IIb, and class III. Class I to III of HDACs are homologous with yeast RPD3, Hda1, and Sir2 family of deacetylases, respectively. HDAC1 to 3 and 8 belong to Class I, while Class II includes two main isoforms: Class IIa (HDAC4, 5, 7, 9) and Class IIb (HDAC 6, 10), with both shuttling between the nucleus and cytoplasm. There are seven types of HDACs in Class III.

This inhibitor of HDACs can block the activity of HDAC by chelating the zinc co-enzyme factor. This results in the hyperacetylation of the lysine residues of the histone. Currently, HDACi can be divided into four groups: short-chain fatty acids, cyclic tetrapeptides, benzamides, and the most common type, hydroxamic acids [104, 105]. An approved drug-targeted hydroxamic acid, suberoylanilide hydroxamic acid has been used in clinical anti-cancer therapy. HDACi is involved in anti-cancer effects in multiple ways, including by affecting cell mitosis, affecting DNA repairing, and improving sensitivity to tumor treatment. For instance, CG-1521 acts as an inhibitor of HDAC to block mitotic spindle formation and impede abscission during the cytokinesis of inflammatory breast cancer. Sodium butyrate, another HDACi, can suppress DNA double-strand break repair, which promotes the cell death of MCF-7 cells [106]. Entinostat, a class I HDACi, has been reported to enhance the

Table 2: The enzymes of acetylation/deacetylation and methylation and demethylation.

Type	Regulators/enzymes	Function	Reference
Acetylation	**Histone acetyltransferases (HATs)**		
	GNAT Family (GCN5-related N-acetyltransferases): GCN5 (KAT2A), PCAF (KAT2B)	Involved in transcriptional activation by acetylating histones H3 and H4, which loosens chromatin structure and facilitates transcription factor binding.	[108]
	p300/CBP Family: p300 (EP300), CBP (CREBBP)	These have broad transcriptional coactivator functions. They acetylate a wide range of histone (e.g., H3 and H4) and non-histone proteins, regulating processes such as cell cycle progression, DNA repair, and cell differentiation.	[109]
	MYST Family: MOZ (KAT6A), MORF (KAT6B), Tip60 (KAT5), HBO1 (KAT7), MOF (KAT8)	Members of this family are involved in various cellular processes, including cell cycle regulation, DNA damage repair, and cell differentiation. For example, Tip60 acetylates H4 and H2AX, playing a crucial role in the DNA damage response.	[110–113]
	HAT1	The first HAT discovered, primarily acetylates newly synthesized histone H4 in the cytoplasm at lysine 12 (K12). This acetylation is important for the assembly of histone H3-H4 dimers into nucleosomes and chromatin formation.	[114]
	Non-histone acetyltransferases		
	p300/CBP	While p300 (EP300) and CBP (CREBBP) also acetylate histones, they have broad specificity and can acetylate numerous non-histone proteins, including transcription factors like p53, thereby regulating their activity, DNA-binding affinity, and stability. This acetylation plays a critical role in cell cycle regulation and differentiation.	[115, 116]
	PCAF (P300/CBP-Associated Factor)	Similar to p300/CBP, PCAF can acetylate both histone and non-histone proteins, including p53. PCAF is involved in the regulation of transcription, cell cycle progression, and apoptosis through its acetylation targets.	[117, 118]
	NATs (N-Acetyltransferases)	This family includes several enzymes that acetylate the N-terminus of proteins, a modification that can affect protein stability, localization, and interaction with other molecules. N-terminal acetylation is a common modification that affects a significant portion of the eukaryotic proteome.	
	MYST Family	Although known for their roles in histone acetylation, members of the MYST family, such as MOF (KAT8), also target non-histone proteins. For example, MOF can acetylate p53 and is involved in DNA damage response and maintenance of stem cell identity.	[119, 120]
	GCN5 (General Control Non-derepressible 5)	Besides histones, GCN5 (KAT2A) acetylates non-histone proteins involved in transcription regulation, such as TFIID, thus influencing transcription initiation and gene expression.	[121]
Deacetylation	**Histone deacetylases (HDACs)**		
	Class I HDACs: HDAC1, HDAC2, HDAC3, and HDAC8	They are involved in the regulation of gene expression and are crucial for cell cycle progression and differentiation.	[122–125]
	Class II HDACs: Subdivided into Class IIa (HDAC4, HDAC5, HDAC7, HDAC9) and Class IIb (HDAC6, HDAC10)	Class IIa HDACs are involved in tissue-specific gene expression and developmental processes. Class IIb HDACs, particularly HDAC6, have a unique role in cytoplasmic structures and are involved in the regulation of cell motility, autophagy, and stress response.	[126–129]
	Class III HDACs (Sirtuins): SIRT1-SIRT7	Sirtuins are involved in the regulation of metabolism, stress responses, and longevity. They require NAD+ for their deacetylase activity, linking their activity to the cellular metabolic state.	[130–133]
	Class IV HDAC: HDAC11	HDAC11 has been implicated in both gene repression and activation, but its specific roles are less well understood compared to other classes.	[134]
Methylation	**DNA Methyltransferases (DNMTs)**		
	DNMT1	Maintains methylation patterns after DNA replication by copying methylation marks from the parent strand to the daughter strand, ensuring the heritability of epigenetic information.	[135]

Table 2: (continued)

Type	Regulators/enzymes	Function	Reference
	DNMT3A and DNMT3B	Responsible for *de novo* methylation, establishing new DNA methylation patterns during development and in differentiated tissues.	[136, 137]
	DNMT3L	Lacks enzymatic activity but is crucial for the establishment of maternal genomic imprints; acts as a stimulatory factor for DNMT3A and DNMT3B.	[136]
	Histone Methyltransferases (HMTs)		
	EZH2 (Enhancer of Zeste Homolog 2)	Part of the polycomb repressive complex 2 (PRC2), which trimethylates histone H3 on lysine 27 (H3K27me3), leads to transcriptional repression of target genes.	[138]
	SUV39H1 (Suppressor of Variegation 3-9 Homolog 1)	Methylates histone H3 on lysine 9 (H3K9me3), a mark associated with heterochromatin formation and gene silencing.	[139]
	DOT1L (Disruptor of Telomeric Silencing 1-Like)	The only known enzyme that methylates histone H3 on lysine 79 (H3K79), is involved in transcriptional activation and repression, as well as DNA damage response.	[140]
	RNA Methyltransferases		
	METTL3	The main catalytic component of the m^6A methyltransferase complex, responsible for the N^6-methyladenosine (m^6A) modification on RNA, which affects RNA stability, translation efficiency, and splicing.	[141]
	METTL14	Works closely with METTL3 as part of the m6A methyltransferase complex, contributing to the recognition of RNA substrates but with limited catalytic activity on its own.	[142]
	WTAP (Wilms Tumor 1 Associated Protein)	Although not a methyltransferase itself, WTAP is an essential regulatory subunit of the m^6A methyltransferase complex, influencing the localization and substrate specificity of the complex.	[143]
	METTL16	Methylates the U6 small nuclear RNA (snRNA) and a subset of mRNAs, playing roles in splicing regulation and other RNA processing events.	[144]
	KIAA1429 (VIRMA, Virus-Responsive Molecule A)	KIAA1429 is vital for directing the m6A methyltransferase complex to specific RNA regions, especially around the stop codon and the 3′ untranslated regions (3′UTRs), thereby influencing the m^6A modification landscape on mRNA. This modification impacts mRNA stability, translation, and nuclear export.	[145]
	RBM15 (RNA binding motif protein 15)	RBM15 acts as an adaptor protein within the m^6A methyltransferase complex, guiding the complex to RNA substrates for methylation. It is involved in RNA processing events like alternative splicing and plays a role in X chromosome inactivation.	[146]
	ZC3H13 (Zinc Finger CCCH-Type Containing 13)	ZC3H13 is crucial for anchoring the m^6A methyltransferase complex within the nucleus, facilitating the methylation of nuclear RNAs. It plays a significant role in RNA processing and export, impacting gene expression regulation.	[147]
Demethylation	**Histone Demethylases**		
	LSD1 (Lysine-Specific Demethylase 1)	Demethylates mono- and dimethylated lysine 4 of histone H3 (H3K4me1/2), usually leading to transcriptional repression.	[148]
	JHDMs (Jumonji C-Domain-Containing Histone Demethylases)	A large family of enzymes that can remove methyl groups from various lysine residues on histones, including H3K9, H3K27, H3K36, and H4K20, thereby regulating gene expression positively or negatively depending on the specific lysine residue demethylated.	[149]
	DNA Demethylases		
	TET Enzymes (Ten-Eleven Translocation)	Convert 5-methylcytosine (m^5C) to 5-hydroxymethylcytosine (5hmC) and further oxidation products, facilitating DNA demethylation. This process is important for active DNA demethylation, embryonic development, and cellular differentiation.	[150]
	RNA Demethylases		
	FTO (Fat Mass and Obesity-Associated Protein)	The first identified m^6A demethylase, capable of removing m^6A modifications from RNA, thereby influencing RNA metabolism and processing, including mRNA stability and splicing.	[151]

Table 2: (continued)

Type	Regulators/enzymes	Function	Reference
	ALKBH5 (AlkB Homolog 5)	Another m^6A demethylase that specifically demethylates m^6A in mRNA and non-coding RNA, affecting RNA metabolism, export, and decay, as well as the regulation of gene expression and cellular stress response.	[152]
	NSUN2 (NOP2/Sun RNA Methyltransferase Family, Member 2)	Catalyzes the formation of m^5C in various RNAs, including tRNAs, mRNAs, and non-coding RNAs, affecting RNA stability and translation.	[153, 154]
	TRMT6/61A (TRNA Methyltransferase 6/61A)	Responsible for the N^1-methyladenosine (m^1A) modification in tRNAs, influencing tRNA stability and the efficiency of protein synthesis.	[155]

sensitivity of breast cancer to lapatinib through FOXO3-mediated Bim1 expression [107]. In addition, HDACi can regulate cell growth and the cell cycle and is involved in DNA repair, indicating that it shows good prospects in cancer therapy (Table 2).

The dilemma of research on drug targeting histone methylation or acetylation

Although the inhibition of histone methylation or acetylation has been shown to be promising for cancer treatment, the efficacy of some inhibitors needs to be enhanced. Owing to the reversible nature of epigenetic modifications, certain inhibitors need to be taken continuously to achieve maximal antitumor effects and clinical response. There are many factors that adversely affect the bioavailability and antitumor activity of the inhibitors, including rapid metabolism, a high degree of protein binding, rapid inactivation of reactive functional groups, and rapid clearance. For instance, it has been reported that butyrate and phenylbutyrate are rapidly degraded after intravenous administration, indicating that continuous venous transfusion for 120 days at a dose of ≥400 mg/kg/day is needed for some clinical trials [156]. Chemical modifications may be a good method to increase efficacy. For instance, the natural inhibitor, S-adenosylhomocysteine (SAH), exhibits inhibitory activity against DOT1L with a Ki value of 260 nM. A valid methodology for inhibiting the activity of DOT1L is by replacing the sidechain in SAH with a tert-butylphenyl urea containing a tertiary amine group. The Ki value, 0.3 nM, is about 860-fold higher than the activity of SAH. However, since the proteins that control histone methylation or acetylation are relatively homologous with each other, most cofactors used in this process are the same, and problems have been encountered with the discovery of more highly selective small molecule inhibitors. Currently, research on potent inhibitors has often ended in failure in clinical trials and the cost is high. Therefore, high-throughput screening, as well as the designing and synthesis of inhibitors need to be performed.

It is necessary to know the association between cancer therapy targets and histone modifying enzymes before designing and synthesizing inhibitors. Genetic screening of gene mutations may offer a valuable method of identifying potential targets in clinical tissues. The clinical correlation and mechanisms by which mutation functions to exert pathogenesis also require profound studies. Epigenetic therapies lack specificity; some inhibitors have low efficacy when used alone. HDACi has already been used in combination with immunotherapy, showing slower tumor growth in combination with the HDACi, Panobinostat, and anti-PD-1 antibody therapy. This novel approach to cancer needs more trials to be conducted.

Therefore, we should pay close attention to the underlying potential toxic effects caused by the inhibition of histone methylation or acetylation enzymes, since these two modifications also appear in normal physiology. For instance, an inhibitor of LSD1 could play an anti-cancer function in MLL-AF9 transformed leukemic stem cells by decreasing leukemia-relevant gene expression [157]. However, in an MLL-AF9 leukemia mouse model, this inhibitor showed severe systemic toxicities with unclear mechanisms. Therefore, toxicological studies need to be conducted to confirm this result.

Conclusions

In recent years, the role and regulation of histone methylation and acetylation in cancer and the mechanism of drug action have been thoroughly discussed. Along with advancements in research, targeted modification enzyme inhibitors have become a hot research focus in cancer therapy. Research on epigenetic-targeted drugs is still in its infancy. Many efforts are needed in the fields of dominant

biology, structural biology, and pharmacodynamics. Clinically unmanageable toxicities should not be ignored. To accelerate the development of epigenetic drugs, epigenetic chemical probes, assays, antibodies, and X-ray crystal structures have been connected, and is known as the Structural Genomics Consortium (SGC). SGC provides a resource-sharing platform for the application of 3D protein structures to genomics and advancements of the discovery of small-molecule targeted drugs [158]. Moreover, the sequencing of patients with tumors can help to identify epigenetic targets and determine sensitivities to therapeutic interventions. Overall, these studies can help us understand the role of histone modifications and related enzymes in cancer initiation and progression, and provide a theoretical basis that can be used to enhance cancer treatment.

Acknowledgments: We thank all authors prepared, written, reviewed and edited the entire manuscript.
Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: Su Bu and Ting Ye wrote the paper; Hang Gao retrieved documents and designed illustrations; Hang Song and Yong-fu Zhu conceived and designed the article. All authors have read and approved the manuscript.
Use of Large Language Models, AI and Machine Learning Tools: None declared.
Conflict of interest: We have no conflict of interest to declare.
Research funding: This research was funded by Project of High-Level Talents in AHUTCM [2019rcZD001]; Clinical science research project of the First Affiliated Hospital of Anhui University of Chinese Medicine [2020yfyzc06]; Scientific research project of Anhui University of Traditional Chinese Medicine [2022AH050415]; Horizontal scientific research Project [2021HZ002 and 2022HZ009] and Key Project of Anhui Provincial Department of Education [2023AH050870].
Data availability: Not applicable.

References

1. Kumar R, Li DQ, Müller S, Knapp S. Epigenomic regulation of oncogenesis by chromatin remodeling. Oncogene 2016;35:4423–36.
2. Ning B, Li W, Zhao W, Wang R. Targeting epigenetic regulations in cancer. Acta Bioch Bioph Sina 2016;48:97–109.
3. Dhaenens M. Histone clipping: the punctuation in the histone code. EMBO Rep 2021;22:e53440.
4. You H, Li Q, Kong D, Liu X, Kong F, Zheng K, et al. The interaction of canonical Wnt/beta-catenin signaling with protein lysine acetylation. Cell Mol Biol Lett 2022;27:7.
5. Gu Y, Zhang X, Yu W, Dong W. Oncogene or tumor suppressor: the coordinative role of lysine methyltransferase SET7/9 in cancer development and the related mechanisms. J Cancer 2022;13:623–40.
6. Wang YS, Chen C, Ahmad MJ, Chen F, Ding ZM, Yang SJ, et al. WDR62 regulates mouse oocyte meiotic maturation related to p-JNK and H3K9 trimethylation. Int J Biochem Cell Biol 2022;144:106169.
7. Fujii K, Idogawa M, Suzuki N, Iwatsuki K, Kanekura T. Functional depletion of HSP72 by siRNA and quercetin enhances vorinostat-induced apoptosis in an HSP72-overexpressing cutaneous T-cell lymphoma cell line, Hut78. Int J Mol Sci 2021;22:11258.
8. Feng Y, Endo M, Sugiyama H. Nucleosomes and epigenetics from a chemical perspective. Chembiochem 2021;22:595–612.
9. Toyobe M, Yakushiji F. Synthetic modifications of histones and their functional evaluation. Chem Asian J 2022;17:e202200197.
10. Demetriadou C, Koufaris C, Kirmizis A. Histone N-alpha terminal modifications: genome regulation at the tip of the tail. Epigenet Chromatin 2020;13:29.
11. Chen YC, Koutelou E, Dent SYR. Now open: evolving insights to the roles of lysine acetylation in chromatin organization and function. Mol Cell 2022;82:716–27.
12. Morrison AJ. Chromatin-remodeling links metabolic signaling to gene expression. Mol Metab 2020;38:100973.
13. Xie X, Wu Q, Zhang K, Liu Y, Zhang N, Chen Q, et al. O-GlcNAc modification regulates MTA1 transcriptional activity during breast cancer cell genotoxic adaptation. Biochim Biophys Acta Gen Subj 2021; 1865:129930.
14. Roberti A, Valdes AF, Torrecillas R, Fraga MF, Fernandez AF. Epigenetics in cancer therapy and nanomedicine. Clin Epigenet 2019; 11:81.
15. Taniue K, Hayashi T, Kamoshida Y, Kurimoto A, Takeda Y, Negishi L, et al. UHRF1-KAT7-mediated regulation of TUSC3 expression via histone methylation/acetylation is critical for the proliferation of colon cancer cells. Oncogene 2020;39:1018–30.
16. Zhang Z, Wan R, Yuan Q, Dou H, Tu P, Shi D, et al. Cell damage and neutrophils promote the infection of Mycoplasma pneumoniae and inflammatory response. Microb Pathog 2022;169:105647.
17. Chang S, Yim S, Park H. The cancer driver genes IDH1/2, JARID1C/KDM5C, and UTX/KDM6A: crosstalk between histone demethylation and hypoxic reprogramming in cancer metabolism. Exp Mol Med 2019;51:1–17.
18. Shan CM, Kim JK, Wang J, Bao K, Sun Y, Chen H, et al. The histone H3K9M mutation synergizes with H3K14 ubiquitylation to selectively sequester histone H3K9 methyltransferase Clr4 at heterochromatin. Cell Rep 2021;35:109137.
19. Hisanaga T, Romani F, Wu S, Kowar T, Wu Y, Lintermann R, et al. The Polycomb repressive complex 2 deposits H3K27me3 and represses transposable elements in a broad range of eukaryotes. Curr Biol 2023; 33:4367–80 e9.
20. Sasidharan Nair V, El Salhat H, Taha RZ, John A, Ali BR, Elkord E. DNA methylation and repressive H3K9 and H3K27 trimethylation in the promoter regions of PD-1, CTLA-4, TIM-3, LAG-3, TIGIT, and PD-L1 genes in human primary breast cancer. Clin Epigenet 2018;10:78.
21. Sasidharan Nair V, Toor SM, Taha RZ, Shaath H, Elkord E. DNA methylation and repressive histones in the promoters of PD-1, CTLA-4, TIM-3, LAG-3, TIGIT, PD-L1, and galectin-9 genes in human colorectal cancer. Clin Epigenet 2018;10:104.
22. Zou L Heterochromatin-dependent replication stress: a lesson from IDH1/2 mutants. Cancer Res 2023;83:2987–9.
23. Wu D, Qiu Y, Jiao Y, Qiu Z, Liu D. Small molecules targeting HATs, HDACs, and BRDs in cancer therapy. Front Oncol 2020;10:560487.
24. Choudhary C, Kumar C, Gnad F, Nielsen ML, Rehman M, Walther TC, et al. Lysine acetylation targets protein complexes and co-regulates major cellular functions. Science 2009;325:834–40.

25. Hintzen JCJ, Merx J, Maas MN, Langens S, White PB, Boltje TJ, et al. Amide-derived lysine analogues as substrates and inhibitors of histone lysine methyltransferases and acetyltransferases. Org Biomol Chem 2021;20:173–81.
26. Xu Y, Liao W, Luo Q, Yang D, Pan M. Histone acetylation regulator-mediated acetylation patterns define tumor malignant pathways and tumor microenvironment in hepatocellular carcinoma. Front Immunol 2022;13:761046.
27. Zhang L, Gai Y, Liu Y, Meng D, Zeng Y, Luo Y, et al. Tau induces inflammasome activation and microgliosis through acetylating NLRP3. Clin Transl Med 2024;14:e1623.
28. Fan P, Zhao J, Meng Z, Wu H, Wang B, Wu H, et al. Overexpressed histone acetyltransferase 1 regulates cancer immunity by increasing programmed death-ligand 1 expression in pancreatic cancer. J Exp Clin Cancer Res 2019;38:47.
29. Cheng Y, He C, Wang M, Ma X, Mo F, Yang S, et al. Targeting epigenetic regulators for cancer therapy: mechanisms and advances in clinical trials. Signal Transduct Targeted Ther 2019;4:62.
30. Rani N, Sahu M, Ambasta RK, Kumar P. Triaging between post-translational modification of cell cycle regulators and their therapeutics in neurodegenerative diseases. Ageing Res Rev 2024;94: 102174.
31. Hogg SJ, Motorna O, Cluse LA, Johanson TM, Coughlan HD, Raviram R, et al. Targeting histone acetylation dynamics and oncogenic transcription by catalytic P300/CBP inhibition. Mol Cell 2021;81: 2183–200 e13.
32. Wang Y, Ha M, Li M, Zhang L, Chen Y. Histone deacetylase 6-mediated downregulation of TMEM100 expedites the development and progression of non-small cell lung cancer. Hum Cell 2022;35:271–85.
33. Hentschel AE, Beijert IJ, Bosschieter J, Kauer PC, Vis AN, Lissenberg-Witte BI, et al. Bladder cancer detection in urine using DNA methylation markers: a technical and prospective preclinical validation. Clin Epigenet 2022;14:19.
34. Liu C, Yang Q, Zhu Q, Lu X, Li M, Hou T, et al. CBP mediated DOT1L acetylation confers DOT1L stability and promotes cancer metastasis. Theranostics 2020;10:1758–76.
35. Shan L, Hao C, Jun Z, Qinghe C. Histone methyltransferase Dot1L inhibits pancreatic cancer cell apoptosis by promoting NUPR1 expression. J Int Med Res 2022;50:3000605221088431.
36. Song Z, Wei Z, Wang Q, Zhang X, Tao X, Wu N, et al. The role of DOT1L in the proliferation and prognosis of gastric cancer. Biosci Rep 2020;40: BSR20193515.
37. Zhang X, Liu D, Li M, Cao C, Wan D, Xi B, et al. Prognostic and therapeutic value of disruptor of telomeric silencing-1-like (DOT1L) expression in patients with ovarian cancer. J Hematol Oncol 2017;10:29.
38. Sonoda Y, Itoh M, Tohda S. Effects of HOXA9 inhibitor DB818 on the growth of acute myeloid leukaemia cells. Anticancer Res 2021;41: 1841–7.
39. Zha JP, Wang XQ, Di J. MiR-920 promotes osteogenic differentiation of human bone mesenchymal stem cells by targeting HOXA7. J Orthop Surg Res 2020;15:254.
40. Meriç N, Kocabaş F. The historical relationship between Meis1 and leukemia. Adv Exp Med Biol 2022;1387:127–44.
41. Blasi F, Bruckmann C. MEIS1 in hematopoiesis and cancer. How MEIS1-PBX interaction can Be used in therapy. J Dev Biol 2021;9:44.
42. Bunse L, Platten M. How mutant isocitrate dehydrogenase orchestrates immune cells. Neuro Oncol 2022;24:210–2.
43. Galanis E, Wen PY, de Groot JF, Weller M. Isocitrate dehydrogenase wild-type glial tumors, including glioblastoma. Hematol Oncol Clin N Am 2022;36:113–32.
44. Lachowiez C, DiNardo CD, Stein E. Combining isocitrate dehydrogenase inhibitors with existing regimens in acute myeloid leukemia: an evolving treatment landscape. Cancer J 2022;28:21–8.
45. Andrews C, Prayson RA. IDH mutations in older patients with diffuse astrocytic gliomas. Ann Diagn Pathol 2020;49:151653.
46. Yang Q, Hao J, Chi M, Wang Y, Li J, Huang J, et al. D2HGDH-mediated D2HG catabolism enhances the anti-tumor activities of CAR-T cells in an immunosuppressive microenvironment. Mol Ther 2022;30: 1188–200.
47. Singh P, Bhadada SK, Dahiya D, Saikia UN, Arya AK, Sachdeva N, et al. GCM2 silencing in parathyroid adenoma is associated with promoter hypermethylation and gain of methylation on histone 3. J Clin Endocrinol Metab 2021;106:e4084–e96.
48. Fain JS, Loriot A, Diacofotaki A, Van Tongelen A, De Smet C. Transcriptional overlap links DNA hypomethylation with DNA hypermethylation at adjacent promoters in cancer. Sci Rep 2021;11:17346.
49. Nguyen K, Dobrowolski C, Shukla M, Cho WK, Luttge B, Karn J. Inhibition of the H3K27 demethylase UTX enhances the epigenetic silencing of HIV proviruses and induces HIV-1 DNA hypermethylation but fails to permanently block HIV reactivation. PLoS Pathog 2021;17:e1010014.
50. Yu J, Chai P, Xie M, Ge S, Ruan J, Fan X, et al. Histone lactylation drives oncogenesis by facilitating m(6)A reader protein YTHDF2 expression in ocular melanoma. Genome Biol 2021;22:85.
51. Ma X, Fan Y, Xiao W, Ding X, Hu W, Xia Y. Glufosinate-ammonium induced aberrant histone modifications in mouse sperm are concordant with transcriptome in preimplantation embryos. Front Physiol 2021;12:819856.
52. Zhang J, Gao X, Yu L. Roles of histone deacetylases in acute myeloid leukemia with fusion proteins. Front Oncol 2021;11:741746.
53. Li S, Yang X, Liu S, Chen Y, Xing H, Tang K, et al. A novel fusion protein TBLR1-RARα acts as an oncogene to induce murine promyelocytic leukemia: identification and treatment strategies. Cell Death Dis 2021; 12:607.
54. Wei S, Liu W, Sun N, Wu Y, Song H, Wang C, et al. MOF upregulates the estrogen receptor α signaling pathway by its acetylase activity in hepatocellular carcinoma. Cancer Sci 2021;112:1865–77.
55. Li Y, Chen X, Lu C. The interplay between DNA and histone methylation: molecular mechanisms and disease implications. EMBO Rep 2021;22:e51803.
56. Osako T, Lee H, Turashvili G, Chiu D, McKinney S, Joosten SEP, et al. Age-correlated protein and transcript expression in breast cancer and normal breast tissues is dominated by host endocrine effects. Nat Cancer 2020;1:518–32.
57. Bae AN, Jung SJ, Lee JH, Lee H, Park SG. Clinical value of EZH2 in hepatocellular carcinoma and its potential for target therapy. Medicina 2022;58:155.
58. Gorodetska I, Lukiyanchuk V, Peitzsch C, Kozeretska I, Dubrovska A. BRCA1 and EZH2 cooperate in regulation of prostate cancer stem cell phenotype. Int J Cancer 2019;145:2974–85.
59. Yin X, Yang S, Zhang M, Yue Y. The role and prospect of JMJD3 in stem cells and cancer. Biomed Pharmacother 2019;118:109384.
60. Sneeringer CJ, Scott MP, Kuntz KW, Knutson SK, Pollock RM, Richon VM, et al. Coordinated activities of wild-type plus mutant EZH2 drive tumor-associated hypertrimethylation of lysine 27 on histone H3 (H3K27) in human B-cell lymphomas. Proc Natl Acad Sci U S A 2010;107: 20980–5.
61. Chu MQ, Zhang TJ, Xu ZJ, Gu Y, Ma JC, Zhang W, et al. EZH2 dysregulation: potential biomarkers predicting prognosis and guiding treatment choice in acute myeloid leukaemia. J Cell Mol Med 2020;24: 1640–9.

62. Izutsu K, Ando K, Nishikori M, Shibayama H, Teshima T, Kuroda J, et al. Phase II study of tazemetostat for relapsed or refractory B-cell non-Hodgkin lymphoma with EZH2 mutation in Japan. Cancer Sci 2021;112: 3627–35.
63. Mu W, Starmer J, Yee D, Magnuson T. EZH2 variants differentially regulate polycomb repressive complex 2 in histone methylation and cell differentiation. Epigenet Chromatin 2018;11:71.
64. Akpa CA, Kleo K, Oker E, Tomaszewski N, Messerschmidt C, López C, et al. Acquired resistance to DZNep-mediated apoptosis is associated with copy number gains of AHCY in a B-cell lymphoma model. BMC Cancer 2020;20:427.
65. Zhu K, Du D, Yang R, Tao H, Zhang H. Identification and assessments of novel and potent small-molecule inhibitors of EED-EZH2 interaction of polycomb repressive complex 2 by computational methods and biological evaluations. Chem Pharm Bull 2020;68:58–63.
66. Kohashi K, Yamamoto H, Yamada Y, Kinoshita I, Taguchi T, Iwamoto Y, et al. SWI/SNF chromatin-remodeling complex status in SMARCB1/INI1-preserved epithelioid sarcoma. Am J Surg Pathol 2018;42:312–8.
67. Gluckstein MI, Dintner S, Arndt TT, Vlasenko D, Schenkirsch G, Agaimy A, et al. Comprehensive immunohistochemical study of the SWI/SNF complex expression status in gastric cancer reveals an adverse prognosis of SWI/SNF deficiency in genomically stable gastric carcinomas. Cancers 2021;13:3894.
68. Xing Z, Ma B, Sun W, Sun Y, Liu C. Comprehensive characterization and clinical relevance of the SWI/SNF copy number aberrations across human cancers. Hereditas 2021;158:38.
69. Simeone N, Frezza AM, Zaffaroni N, Stacchiotti S. Tazemetostat for advanced epithelioid sarcoma: current status and future perspectives. Future Oncol 2021;17:1253–63.
70. Morschhauser F, Tilly H, Chaidos A, McKay P, Phillips T, Assouline S, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. Lancet Oncol 2020;21:1433–42.
71. Li ZR, Suo FZ, Guo YJ, Cheng HF, Niu SH, Shen DD, et al. Natural protoberberine alkaloids, identified as potent selective LSD1 inhibitors, induce AML cell differentiation. Bioorg Chem 2020;97: 103648.
72. Carmichael CL, Wang J, Nguyen T, Kolawole O, Benyoucef A, De Maziere C, et al. The EMT modulator SNAI1 contributes to AML pathogenesis via its interaction with LSD1. Blood 2020;136:957–73.
73. Xie Q, Tang T, Pang J, Xu J, Yang X, Wang L, et al. LSD1 promotes bladder cancer progression by upregulating LEF1 and enhancing EMT. Front Oncol 2020;10:1234.
74. Bansal AK, Sharawat SK, Gupta R, Vishnubhatla S, Dhawan D, Bakhshi S. Regulatory T cells in pediatric AML are associated with disease load and their serial assessment suggests role in leukemogenesis. Am J Blood Res 2020;10:90–6.
75. Lu Z, Guo Y, Zhang X, Li J, Li L, Zhang S, et al. ORY-1001 suppresses cell growth and induces apoptosis in lung cancer through triggering HK2 mediated Warburg effect. Front Pharmacol 2018;9:1411.
76. Cuyàs E, Gumuzio J, Verdura S, Brunet J, Bosch-Barrera J, Martin-Castillo B, et al. The LSD1 inhibitor iadademstat (ORY-1001) targets SOX2-driven breast cancer stem cells: a potential epigenetic therapy in luminal-B and HER2-positive breast cancer subtypes. Aging 2020;12: 4794–814.
77. Gerrard DL, Boyd JR, Stein GS, Jin VX, Frietze S. Disruption of broad epigenetic domains in PDAC cells by HAT inhibitors. Epigenomes 2019; 3:11.
78. Zhou M, Yuan M, Zhang M, Lei C, Aras O, Zhang X, et al. Combining histone deacetylase inhibitors (HDACis) with other therapies for cancer therapy. Eur J Med Chem 2021;226:113825.
79. Mantzourani C, Gkikas D, Kokotos A, Nummela P, Theodoropoulou MA, Wu KC, et al. Synthesis of benzoxazole-based vorinostat analogs and their antiproliferative activity. Bioorg Chem 2021;114:105132.
80. Karol SE, Cooper TM, Mead PE, Crews KR, Panetta JC, Alexander TB, et al. Safety, pharmacokinetics, and pharmacodynamics of panobinostat in children, adolescents, and young adults with relapsed acute myeloid leukemia. Cancer 2020;126:4800–5.
81. Willcockson MA, Healton SE, Weiss CN, Bartholdy BA, Botbol Y, Mishra LN, et al. H1 histones control the epigenetic landscape by local chromatin compaction. Nature 2021;589:293–8.
82. Roussos TET, Ho WJ, Danilova L, Tandurella JA, Leatherman J, Rafie C, et al. Entinostat, nivolumab and ipilimumab for women with advanced HER2-negative breast cancer: a phase Ib trial. Nat Cancer 2024;5: 866–79.
83. Gibbons GS, Chakraborty A, Grigsby SM, Umeano AC, Liao C, Moukha-Chafiq O, et al. Identification of DOT1L inhibitors by structure-based virtual screening adapted from a nucleoside-focused library. Eur J Med Chem 2020;189:112023.
84. Cao M, Li T, Chen Y, Zhai X. Nucleoside and non-nucleoside DOT1L inhibitors: dawn of MLLrearranged leukemia. Mini Rev Med Chem 2021;21:1337–50.
85. Heimbruch KE, Fisher JB, Stelloh CT, Phillips E, Reimer MH Jr., Wargolet AJ, et al. DOT1L inhibitors block abnormal self-renewal induced by cohesin loss. Sci Rep 2021;11:7288.
86. Stauffer F, Weiss A, Scheufler C, Mobitz H, Ragot C, Beyer KS, et al. New potent DOT1L inhibitors for in vivo evaluation in mouse. ACS Med Chem Lett 2019;10:1655–60.
87. Stein EM, Garcia-Manero G, Rizzieri DA, Tibes R, Berdeja JG, Savona MR, et al. The DOT1L inhibitor pinometostat reduces H3K79 methylation and has modest clinical activity in adult acute leukemia. Blood 2018;131:2661–9.
88. Shen DD, Pang JR, Bi YP, Zhao LF, Li YR, Zhao LJ, et al. LSD1 deletion decreases exosomal PD-L1 and restores T-cell response in gastric cancer. Mol Cancer 2022;21:75.
89. Liu W, Zhang Q, Fang Y, Wang Y. The deubiquitinase USP38 affects cellular functions through interacting with LSD1. Biol Res 2018;51:53.
90. Wojtala M, Rybaczek D, Wielgus E, Sobalska-Kwapis M, Strapagiel D, Balcerczyk A. The role of lysine-specific demethylase 1 (LSD1) in shaping the endothelial inflammatory response. Cell Physiol Biochem 2021;55:569–89.
91. Zhang J, Zhao D, Li Q, Du X, Liu Y, Dai X, et al. Upregulation of LSD1 promotes migration and invasion in gastric cancer through facilitating EMT. Cancer Manag Res 2019;11:4481–91.
92. Zhao D, Zhang F, Wang B, Liu B, Li L, Kim SY, et al. Guidelines for clinical diagnosis and treatment of osteonecrosis of the femoral head in adults (2019 version). J Orthop Translat 2020;21:100–10.
93. Xu S, Zheng L, Kang L, Xu H, Gao L. Correction: microRNA-let-7e in serum-derived exosomes inhibits the metastasis of non-small-cell lung cancer in a SUV39H2/LSD1/CDH1-dependent manner. Cancer Gene Ther 2021;28:250–64.
94. Ding L, Wei F, Wang N, Sun Y, Wang Q, Fan X, et al. Tertiary sulphonamide derivatives as dual acting small molecules that inhibit LSD1 and suppress tubulin polymerisation against liver cancer. J Enzym Inhib Med Chem 2021;36:1563–72.

95. Le CQ, Myers G, Habara A, Jearawiriyapaisarn N, Murphy GJ, Chui DHK, et al. Inhibition of LSD1 by small molecule inhibitors stimulates fetal hemoglobin synthesis. Blood 2019;133:2455–9.
96. Liu HM, Suo FZ, Li XB, You YH, Lv CT, Zheng CX, et al. Discovery and synthesis of novel indole derivatives-containing 3-methylenedihydrofuran-2(3H)-one as irreversible LSD1 inhibitors. Eur J Med Chem 2019;175:357–72.
97. Wu F, Zhou C, Yao Y, Wei L, Feng Z, Deng L, et al. 3-(Piperidin-4-ylmethoxy)pyridine containing compounds are potent inhibitors of lysine specific demethylase 1. J Med Chem 2016;59:253–63.
98. Roboz GJ, Yee K, Verma A, Borthakur G, de la Fuente Burguera A, Sanz G, et al. Phase I trials of the lysine-specific demethylase 1 inhibitor, GSK2879552, as mono- and combination-therapy in relapsed/refractory acute myeloid leukemia or high-risk myelodysplastic syndromes. Leuk Lymphoma 2022;63:463–7.
99. White J, Derheimer FA, Jensen-Pergakes K, O'Connell S, Sharma S, Spiegel N, et al. Histone lysine acetyltransferase inhibitors: an emerging class of drugs for cancer therapy. Trends Pharmacol Sci 2024;45:243–54.
100. Shanmugam MK, Dharmarajan A, Warrier S, Bishayee A, Kumar AP, Sethi G, et al. Role of histone acetyltransferase inhibitors in cancer therapy. Adv Protein Chem Struct Biol 2021;125:149–91.
101. Shibahara D, Akanuma N, Kobayashi IS, Heo E, Ando M, Fujii M, et al. TIP60 is required for tumorigenesis in non-small cell lung cancer. Cancer Sci 2023;114:2400–13.
102. Wang X, Wan TC, Kulik KR, Lauth A, Smith BC, Lough JW, et al. Pharmacological inhibition of the acetyltransferase Tip60 mitigates myocardial infarction injury. Dis Model Mech 2023;16:dmm049786.
103. Sanaei M, Kavoosi F. Histone deacetylase inhibitors, intrinsic and extrinsic apoptotic pathways, and epigenetic alterations of histone deacetylases (HDACs) in hepatocellular carcinoma. Iran J Pharm Res 2021;20:324–36.
104. Iveland TS, Hagen L, Sharma A, Sousa MML, Sarno A, Wollen KL, et al. HDACi mediate UNG2 depletion, dysregulated genomic uracil and altered expression of oncoproteins and tumor suppressors in B- and T-cell lines. J Transl Med 2020;18:159.
105. Krasic J, Skara L, Ulamec M, Katusic Bojanac A, Dabelic S, Bulic-Jakus F, et al. Teratoma growth retardation by HDACi treatment of the tumor embryonal source. Cancers 2020;12:3416.
106. Alp E, Damkaci F, Guven E, Tenniswood M. Starch nanoparticles for delivery of the histone deacetylase inhibitor CG-1521 in breast cancer treatment. Int J Nanomed 2019;14:1335–46.
107. Masuda N, Tamura K, Yasojima H, Shimomura A, Sawaki M, Lee MJ, et al. Phase 1 trial of entinostat as monotherapy and combined with exemestane in Japanese patients with hormone receptor-positive advanced breast cancer. BMC Cancer 2021;21:1269.
108. Vannam R, Sayilgan J, Ojeda S, Karakyriakou B, Hu E, Kreuzer J, et al. Targeted degradation of the enhancer lysine acetyltransferases CBP and p300. Cell Chem Biol 2021;28:503–14 e12.
109. Ruhlmann F, Windhof-Jaidhauser IM, Menze C, Beissbarth T, Bohnenberger H, Ghadimi M, et al. The prognostic capacities of CBP and p300 in locally advanced rectal cancer. World J Surg Oncol 2019;17:224.
110. Huang F New KAT6 inhibitors induce senescence and arrest cancer growth. Synth Syst Biotechnol 2018;3:244–5.
111. Zohourian N, Coll E, Dever M, Sheahan A, Burns-Lane P, Brown JAL. Evaluating the cellular roles of the lysine acetyltransferase Tip60 in cancer: a multi-action molecular target for precision oncology. Cancers 2024;16:2677.
112. Yokoyama A, Niida H, Kutateladze TG, Cote J. HBO1, a MYSTerious KAT and its links to cancer. Biochim Biophys Acta Gene Regul Mech 2024;1867:195045.
113. Zhu H, Wang Y, Wei T, Zhao X, Li F, Li Y, et al. KAT8/MOF-Mediated anti-cancer mechanism of gemcitabine in human bladder cancer cells. Biomol Ther 2021;29:184–94.
114. Capone V, Della Torre L, Carannante D, Babaei M, Altucci L, Benedetti R, et al. HAT1: landscape of biological function and role in cancer. Cells 2023;12:1075.
115. Luo J, Chen Z, Qiao Y, Tien JC, Young E, Mannan R, et al. p300/CBP degradation is required to disable the active AR enhanceosome in prostate cancer. bioRxiv 2024:2024.03.29.587346. https://doi.org/10.1101/2024.03.29.587346.
116. Lai R, Lin Z, Yang C, Hai L, Yang Z, Guo L, et al. Novel berberine derivatives as p300 histone acetyltransferase inhibitors in combination treatment for breast cancer. Eur J Med Chem 2024;266:116116.
117. Pan B, Liu C, Su J, Xia C. Activation of AMPK inhibits cervical cancer growth by hyperacetylation of H3K9 through PCAF. Cell Commun Signal 2024;22:306.
118. Cheng YW, Zeng FM, Li DJ, Wang SH, He JZ, Guo ZC, et al. P300/CBP-associated factor (PCAF)-mediated acetylation of Fascin at lysine 471 inhibits its actin-bundling activity and tumor metastasis in esophageal cancer. Cancer Commun 2021;41:1398–416.
119. Zhu R, Chen M, Luo Y, Cheng H, Zhao Z, Zhang M. The role of N-acetyltransferases in cancers. Gene 2024;892:147866.
120. Hernandez-Gonzalez O, Herrera-Vargas DJ, Martinez-Leija ME, Zavala-Reyes D, Portales-Perez DP. The role of arylamine N-acetyltransferases in chronic degenerative diseases: their possible function in the immune system. Biochim Biophys Acta Mol Cell Res 2022;1869:119297.
121. Han Y, Zhao H, Li G, Jia J, Guo H, Tan J, et al. GCN5 mediates DNA-PKcs crotonylation for DNA double-strand break repair and determining cancer radiosensitivity. Br J Cancer 2024;130:1621–34.
122. Naik D, Kalle AM. MicroRNA-mediated epigenetic regulation of HDAC8 and HDAC6: functional significance in cervical cancer. Noncoding RNA Res 2024;9:732–43.
123. Wang Z, Zhao L, Zhang B, Feng J, Wang Y, Zhang B, et al. Discovery of novel polysubstituted N-alkyl acridone analogues as histone deacetylase isoform-selective inhibitors for cancer therapy. J Enzym Inhib Med Chem 2023;38:2206581.
124. Kiweler N, Schwarz H, Nguyen A, Matschos S, Mullins C, Piee-Staffa A, et al. The epigenetic modifier HDAC2 and the checkpoint kinase ATM determine the responses of microsatellite instable colorectal cancer cells to 5-fluorouracil. Cell Biol Toxicol 2023;39:2401–19.
125. Xie N, Mei S, Dai C, Chen W. HDAC1-Mediated downregulation of NEU1 exacerbates the aggressiveness of cervical cancer. Crit Rev Eukaryot Gene Expr 2024;34:45–54.
126. Zhao J, Bai H, Li X, Yan J, Zou G, Wang L, et al. Glucose-sensitive acetylation of Seryl tRNA synthetase regulates lipid synthesis in breast cancer. Signal Transduct Targeted Ther 2021;6:303.
127. OuYang C, Shu G, Liu J, Deng S, Lu P, Li Y, et al. HDAC5, negatively regulated by miR-148a-3p, promotes colon cancer cell migration. Cancer Sci 2022;113:2560–74.
128. Xu L, Wang J, Liu B, Fu J, Zhao Y, Yu S, et al. HDAC9 contributes to serous ovarian cancer progression through regulating epithelial-mesenchymal transition. Biomedicines 2022;10:374.
129. Moi D, Bonanni D, Belluti S, Linciano P, Citarella A, Franchini S, et al. Discovery of potent pyrrolo-pyrimidine and purine HDAC inhibitors for

the treatment of advanced prostate cancer. Eur J Med Chem 2023;260: 115730.
130. Dai W, Zhou J, Jin B, Pan J. Class III-specific HDAC inhibitor Tenovin-6 induces apoptosis, suppresses migration and eliminates cancer stem cells in uveal melanoma. Sci Rep 2016;6:22622.
131. Kumari P, Tarighi S, Fuchshuber E, Li L, Fernandez-Duran I, Wang M, et al. SIRT7 promotes lung cancer progression by destabilizing the tumor suppressor ARF. Proc Natl Acad Sci U S A 2024;121:e2409269121.
132. Liu N, Li Y, Luo G, Jiang M, Liu C, Zhang Y, et al. SIRT6 suppresses colon cancer growth by inducing apoptosis and autophagy through transcriptionally down-regulating Survivin. Mitochondrion 2024;78: 101932.
133. Wang HL, Chen Y, Wang YQ, Tao EW, Tan J, Liu QQ, et al. Sirtuin5 protects colorectal cancer from DNA damage by keeping nucleotide availability. Nat Commun 2022;13:6121.
134. Zhao H, Zhang XM, Xiao S, Wu ZR, Shi YJ, Xie MJ. HDAC11 is related to breast cancer prognosis and inhibits invasion and proliferation of breast cancer cells. Int J Clin Exp Pathol 2023;16:172–83.
135. Karan D, Singh M, Dubey S, Van Veldhuizen PJ, Saunthararajah Y. DNA methyltransferase 1 targeting using guadecitabine inhibits prostate cancer growth by an apoptosis-independent pathway. Cancers 2023; 15:2763.
136. Qaria MA, Xu C, Hu R, Alsubki RA, Ali MY, Sivasamy S, et al. Ectoine globally hypomethylates DNA in skin cells and suppresses cancer proliferation. Mar Drugs 2023;21:621.
137. Cho CC, Lin CJ, Huang HH, Yang WZ, Fei CY, Lin HY, et al. Mechanistic insights into harmine-mediated inhibition of human DNA methyltransferases and prostate cancer cell growth. ACS Chem Biol 2023;18:1335–50.
138. Xiao B, Shi Z, Liu J, Huang Q, Shu K, Liu F, et al. Design, synthesis, and evaluation of VHL-based EZH2 degraders for breast cancer. Bioorg Chem 2024;143:107078.
139. Huang WL, Luo CW, Lin HS, Hung CM, Chen FM, Moi SH, et al. SUV39H1 expression as a guideline for omitting radiotherapy in lymph node-positive triple-negative breast cancer patients. Cancer Genom Proteom 2023;20:582–91.
140. Hou Y, Liu J, Huang S, Wang L, Hu J, Liu X. DOT1L epigenetically regulates autophagy and mitochondria fusion in cell lines of renal cancer. Technol Cancer Res Treat 2023;22:15330338231167249.
141. Jiang X, Liu B, Nie Z, Duan L, Xiong Q, Jin Z, et al. The role of m6A modification in the biological functions and diseases. Signal Transduct Targeted Ther 2021;6:74.
142. Shi B, Liu WW, Yang K, Jiang GM, Wang H. The role, mechanism, and application of RNA methyltransferase METTL14 in gastrointestinal cancer. Mol Cancer 2022;21:163.
143. Huang Q, Mo J, Liao Z, Chen X, Zhang B. The RNA m(6)A writer WTAP in diseases: structure, roles, and mechanisms. Cell Death Dis 2022;13: 852.
144. Satterwhite ER, Mansfield KD. RNA methyltransferase METTL16: targets and function. Wiley Interdiscip Rev RNA 2022;13:e1681.
145. Zhang X, Li MJ, Xia L, Zhang H. The biological function of m6A methyltransferase KIAA1429 and its role in human disease. PeerJ 2022; 10:e14334.
146. Cheng H, Wu J, Li L, Song X, Xue J, Shi Y, et al. RBM15 protects from myocardial infarction by stabilizing NAE1. JACC Basic Transl Sci 2024;9: 631–48.
147. Wen J, Lv R, Ma H, Shen H, He C, Wang J, et al. Zc3h13 regulates nuclear RNA m(6)A methylation and mouse embryonic stem cell self-renewal. Mol Cell 2018;69:1028–38 e6.
148. Johnson JD, Alejo S, Jayamohan S, Sareddy GR. Lysine-specific demethylase 1 as a therapeutic cancer target: observations from preclinical study. Expert Opin Ther Targets 2023;27:1177–88.
149. Manni W, Jianxin X, Weiqi H, Siyuan C, Huashan S. JMJD family proteins in cancer and inflammation. Signal Transduct Targeted Ther 2022;7: 304.
150. Salmeron-Barcenas EG, Zacapala-Gomez AE, Torres-Rojas FI, Antonio-Vejar V, Avila-Lopez PA, Banos-Hernandez CJ, et al. TET enzymes and 5hmC levels in carcinogenesis and progression of breast cancer: potential therapeutic targets. Int J Mol Sci 2023;25:272.
151. Wang F, Hu Y, Wang H, Hu P, Xiong H, Zeng Z, et al. LncRNA FTO-IT1 promotes glycolysis and progression of hepatocellular carcinoma through modulating FTO-mediated N6-methyladenosine modification on GLUT1 and PKM2. J Exp Clin Cancer Res 2023;42:267.
152. Zhang Z, Wang L, Zhao L, Wang Q, Yang C, Zhang M, et al. N6-methyladenosine demethylase ALKBH5 suppresses colorectal cancer progression potentially by decreasing PHF20 mRNA methylation. Clin Transl Med 2022;12:e940.
153. Zou S, Huang Y, Yang Z, Zhang J, Meng M, Zhang Y, et al. NSUN2 promotes colorectal cancer progression by enhancing SKIL mRNA stabilization. Clin Transl Med 2024;14:e1621.
154. Li P, Wang W, Zhou R, Ding Y, Li X. The m(5) C methyltransferase NSUN2 promotes codon-dependent oncogenic translation by stabilising tRNA in anaplastic thyroid cancer. Clin Transl Med 2023;13: e1466.
155. Monshaugen I, Luna L, Rhodes J, Kristiansen FIS, Lang A, Boe SO, et al. Depletion of the m1A writer TRMT6/TRMT61A reduces proliferation and resistance against cellular stress in bladder cancer. Front Oncol 2023;13:1334112.
156. Kleuskens MTA, Haasnoot ML, Herpers BM, Ampting M, Bredenoord AJ, Garssen J, et al. Butyrate and propionate restore interleukin 13-compromised esophageal epithelial barrier function. Allergy 2022;77:1510–21.
157. Fang Y, Yang C, Teng D, Su S, Luo X, Liu Z, et al. Discovery of higenamine as a potent, selective and cellular active natural LSD1 inhibitor for MLL-rearranged leukemia therapy. Bioorg Chem 2021; 109:104723.
158. Morgan Jones M, Chataway J. The Structural Genomics Consortium: successful organisational technology experiment or new institutional infrastructure for health research? Technol Anal Strateg 2021;33: 296–306.