Current Science
CS 6 (2), 6235-6245 (2026)
Received 05 March 2026 | **Accepted 04 April** 2026 | **Online Available 12 April** 2026
https://doi.org/10.52845/CS/2026-6-2-15

Current Science

Current Science

OPEN ACCESS

ISSN (O) 2795-8639

Original Article

Research Progress on the Regulation of Tumor EMT by Dynamic Histone Methylation Modifications

Zhengzhou Luo[1], Yun He[2], Lin Liu[3]

[1]School of Stomatology, Southwest Medical University, Luzhou 646000, China

[2]Department of Oral and Maxillofacial Surgery, The Affiliated Stomatological Hospital, Southwest Medical University, Luzhou 646000, China

[3]Luzhou Key Laboratory of Oral & Maxillofacial Reconstruction and Regeneration, Luzhou 646000, China

***Corresponding Author: Yun He, Lin Liu**

Abstract:
Dynamic histone methylation modifications play a crucial role in regulating gene expression and various biological processes, particularly in tumor initiation and progression. These modifications are primarily achieved through the action of histone methyltransferases and demethylases. A key process in cancer development and progression is epithelial-mesenchymal transition (EMT). However, the regulatory role of dynamic histone methylation modifications in tumor EMT has not yet been fully elucidated. This review elaborates on the role of dynamic histone methylation and demethylation modifications in tumor EMT. Additionally, it summarizes the involvement of related modifying enzymes in cancer therapy.
Keywords: **Methylation;EMT;Tumor**

1. Introduction

Cancer has become a common and frequently occurring disease that seriously endangers human health(1). There are about 6.35 million newly discovered malignant tumors in the world every year, and it is the second largest disease leading to human death(2,3). A critical process in the development of cancer is that tumor cells lose their epithelial differentiation specificity(4). The cell-cell contact is destroyed, leaving the primary tumor and invading surrounding tissues, and then differentiating into new structures(5). This temporary and reversible phenomenon is called epithelial-mesenchymal transformation (EMT). Cancer cells that undergo epithelial-mesenchymal transformation may invade and metastasize, producing the ultimate life-threatening manifestation of cancer progression(6). Thus, epithelial mesenchymal transformation is a process of cancer cell migration, invasion, and metastatic spread that has been extensively studied(7). China focuses on the research of lung cancer, stomach cancer, liver cancer, esophageal cancer, cervical cancer, breast cancer and nasopharyngeal cancer, etc., to study the internal mechanism of action, the most important of which is to control the metastasis of cancer cells, and ultimately achieve the purpose of delaying the development of tumors and even curing tumors.

Epithelial mesenchymal transformation is a biological process in which epithelial cells lose their epithelial characteristics, transform into mesenchymal cells and acquire the ability to invade and metastasize(8). It allows polarized epithelial cells, through basement membrane degradation and mesenchymal cell formation, to undergo a variety of biochemical changes that give them a mesenchymal cell phenotype(9,10). Specifically, it is related to embryo development and organ formation, injury repair and tissue regeneration, and tumor cell invasion and metastasis(11,12).

With the hot research of epigenetics, histone modification serves as a set of universal epigenetic markers involved in dynamic cellular processes (transcription and DNA repair) and chromatin stability maintenance[13]. Among them, the characteristic structure of amino acid residues as part of histones is easily covalently modified by related enzymes, such as methylation and demethylation, histone acetylation and deacetylation, histone phosphorylation and dephosphorylation, ubiquitination, etc[14-19]. Recent studies have shown that histone methylation and demethylation related modification enzymes play a crucial role in epigenetic regulation , participate in gene inhibition and activation, and are an indispensable part of embryonic development[20-24]. Histone methylation is induced by HMTS (methyltransferase), which occurs on the lysine and arginine residues of histones[25]. It is generally believed that the methylation of H3K9, H3K27 and H4K20 mainly occurs at the N terminal of H3 and H4, which can inhibit gene expression. However, methylation of H3K4, H3K36 and H3K79 has an activation effect[26,27]. Moreover, lysine residues can undergo single, double and trimethylation, while arginine residues can undergo single and double methylation[28,29]. These different levels of methylation greatly increase the complexity of histone modification and regulation of gene expression[30]. Methylation has long been considered an irreversible process in histone modification[31]. However, Klose et al reported that there is an enzyme that can remove lysine and arginine methylation in histones[32,33]. This redefines the nature of histone methylation and complicates histone modification pathways. Although significant progress has been made in the study of histone methylation at the protein level, continued research is needed in the molecule areas.

In this review, we summarize the basic knowledge of EMT and histone methylation and demethylation modification, and describe the process of histone methylation and demethylation modification of EMT and the regulation of tumor initiation and progression. In addition, the key role of its related modifying enzymes in tumor therapy is emphasized. Finally, the expectation and potential of the modulatory mechanism for the future treatment of cancer are described.

The role of methylation and demethylation in EMT

In the development of cancer, EMT is considered to be the first step of tumor metastasis. EMT of tumor cells is complicated by histone modification, methylation or demethylation, acetylation or deacetylation, and phosphorylation play an important role in it[34,35]. Studies have shown that histone methylation and demethylation play a key role in EMT[36]. Therefore, this paper mainly explores histone methylation and demethylation in histone modification.

During EMT, down-regulation of the cell adhesion molecule E-cadherin is the most important feature of EMT[37]. Based on this, the role of histone methylation in EMT can be divided into two categories: the first is that histone methylation occurs directly on the epithelial markers of EMT, including E-cadherin, N-cadherin, and vimentin, thereby inducing EMT[38]. The other is the histone methylation modifying enzyme which acts on EMT-TFS and indirectly acts on the epithelial markers of EMT to mediate the occurrence of EMT[39]. Snail (the most common type of EMT-TFS) aggregates in large numbers in the promoter region of E-cadherin gene (CDH1), and then binds to the CDH1 region containing Snail binding original[40]. Snail binds to it and then recruits other EMT-TFs (such as Twist,ZEB, etc.). This results in the blocked translation of E-cadherin, thereby inhibiting EMT. In addition, EMT-TFS can also cooperate with histone methylation related modification enzymes, which together reduce the expression of E-cadherin(Figure1).

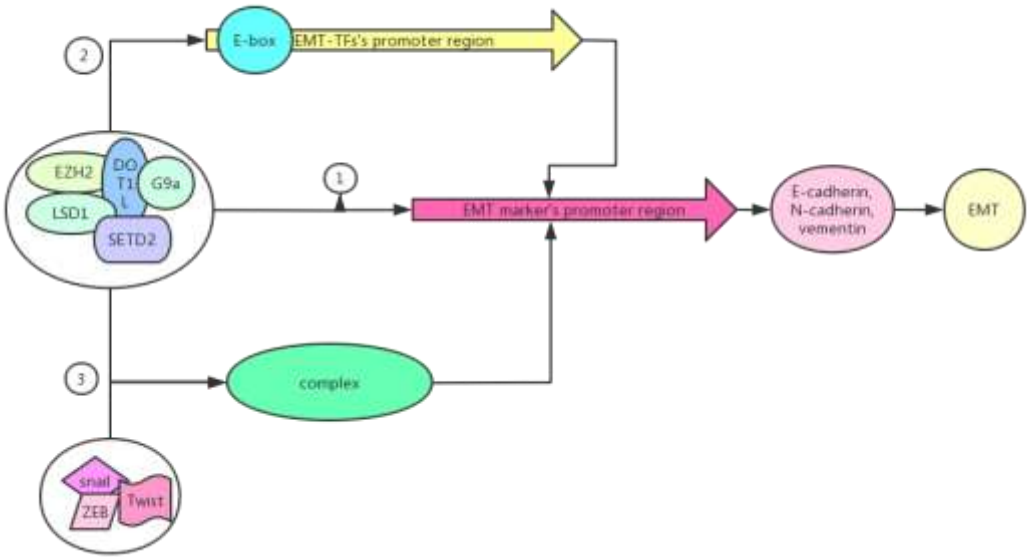

Figure 1 The role of histone methylation in EMT

Methylation and demethylation play a role in tumorigenesis

Methylation or demethylation of histones -- modified by methylases or demethylases -- is an important epigenetic regulator[41]. This regulation mode plays a crucial role in the occurrence, proliferation, transformation and metastasis of cancer. Methylase or demethylase inhibits CDH1 transcription of cancer development process, inhibits the formation of adhesion junctions and desmosomes between cells, and thus induces the invasion and migration of metastatic cancer cells, providing a more clear direction for the research of inhibiting the proliferation of cancer cells. There are also specific recognition of individual enzymes, which can affect hormone secretion, regulate lipid metabolism, and even control cyclin-dependent kinases. For example, An et al. found that a demethylase JMJD2A could inhibit the tumor suppressor gene p21 to enhance the transcription of the amino acid kinase PIML and enhance the expression of PIML, thus affecting the interaction between cyclin-dependent kinase 2(CDK2) and cyclin E (CyclinE)[42]. Induce the G1/S phase inhibition of myeloma cancer cells, thereby promoting the transcription and translation of oncogene (C -- myc), leading to the occurrence of cancer[43].

Histone Methyltransferases

According to the amino acids catalyzed by methyltransferases, HMTs are divided into two categories: histone lysine methyltransferases (KMT) and protein arginine methyltransferases (PRMT)[44]. Among them, more than 50 types of KMT have been reported, and according to their catalytic structural sequence, the KMT family can be classified into the DOT1-like proteins and the SET domain-containing proteins. In KMT, DOT1L is the only protein without a SET domain and its structure is similar to that of arginine methyltransferase[45]. The rest of the lysine methyltransferases belong to the SET domain-containing proteins, which can be divided into four families, namely, SET1, SET2, SUV39, and RIZ, based on the sequence similarity between their SET regions and their adjacent protein regions[46,47].EZH2 has been studied extensively in SET1, SETD2 has been studied extensively in SET2, SUV39H1 and G9A have been studied extensively in SUV39, and RIZ1 has been studied extensively in RIZ[48]. The PRMT family consists of nine members from the mammalian PRMT1-9[49,50].In human cells, Depending on the type of catalytic arginine methylation, These nine members can be divided into three categories[51]. The first is the arginine methyltransferase that catalyzes the ω-NG of monomethyl arginine (MMA) and asymmetric ω-NG、 asymmetric dimethyl arginine (DMA); PRMT1, included 2,3, 4,6, 8. second is methyltransferase that catalyzes MMA and ω、 azide-symmetric dimethyl arginine; PRMT5,

included 9. third is methyltransferase that only catalyzes MMA; Among them PRMT7[52-54]. notably, This classification is also controversial. According to Lee and others, PRMT7 was originally classified as a II PRMT (Table1).

Table 1 Key Histone Methyltransferases in EMT

Emzymes	Effect in EMT	Mechanism	Tumor	Effect in tumor	References
EZH2	induce	H3K27me3	laryngeal squamous cell carcinoma	promotion	55-57
G9a	induce	H3K9me1 H3K9me2	breast tumor	promotion	58-64
SUV39H1	induce	H3K9me3	basal-like breast cancer	promotion	65,66
DOT1L	induce	H3K79me	triple-negative breast cancer	promotion	67-71
SETD2	induce	H3K36me	gastric cancer	promotion	72-75
LSD1	inhibition	H3K4	breast cancer	reduce	88-92

EZH2

The enhancer of zeste homolog 2 (EZH2), known as a member of the polycomb group (PcG) proteins, is a histone methyltransferase. The polycomb repressive complex 2 (PRC2) is a transcriptional regulator catalyzed by EZH2 to participate in X chromosome inactivation, cancer metastasis, and cell differentiation through epigenetic histone modification. A study of laryngeal squamous cell carcinoma revealed that EZH2 could promote cancer invasion and metastasis via EMT through catalysing trimethylation of lysine 27 in histone 3 (H3K27me3) and consequently inducing transcriptional repression of E-cadherin[55,56]. Therefore,EZH2 is closely correlated with tumour aggressiveness in a variety of human malignancies, including oral, nasopharyngeal, gastric, hepatocellular, colon, renal, prostate and lung cancers[57].

G9a

G9a as a methylase can undergo H3K9 monomethylation and dimethylation (H3K9me1 and H3K9me2)[58]. In human cells, G9a has a lot of significant roles. Physically, G9a is necessary for value-added differentiation of embryonic stem cells and immune cells; In pathology, overexpression of G9a can be directly involved in cancer metabolism and anoxic response to promote cancer occurrence and development[59]. In previous studies, G9a is overexpressed in esophageal squamous cell carcinoma, hepatocellular carcinoma, invasive lung cancer, brain cancer, multiple myeloma, and invasive ovarian cancer[60]. The important thing is, Dong's studies have shown that snail can interact with G9a, and were able to recruit G9a and DNA methyltransferases to the E-cadherin promoter region to inhibit their transcription[61]. Moreover, the interaction of snail and G9a is necessary for the enrichment in the E-cadherin promoter and H3K9me2 of G9a[62].When silent expression of G9a, it can inhibit H3K9me2 and DNA methylation, and restore E-cadherin expression, ultimately inhibit breast tumor growth and metastasis[63,64].

SUV39H1

SUV39H1 (Suppressor of Variegation 3 -- 9 Homolog 1) is a histone methyltransferase responsible for the trimethylation of histone H3 at lysine K9 (H3K9M3) in the CDH1 promoter[65]. Similar to G9a, SUV39H1 often interacts with Snail, and this interaction enables SUV39H1 to be recruited to the promoter region of CDH1, thereby inhibiting CDH1 transcription. For example, in a study on basal-like breast cancer (BLBC), H3K9me3 was suppressed by knocking out the SUV39H1 gene to increase E-cadherin expression and inhibit metastasis and invasion of BLBC[66].

DOT1L

Disruptor of Telomeric Silseing-1 Like (DOT1L) is a gene found in the yeast Saccharomyces cerevisia. It's essentially a histone methylation enzyme. DOT1L is the only enzyme responsible for the

monomethylation,dimethylation and trimethylation of H3K79[67]. DOT1L has been shown to play critical roles in human growth and development, including embryonic development, DNA repair, cell cycle regulation, transcriptional regulation, and leukemia development. Recent studies have shown that abnormal methylation of histone H3 lysine 79 residues (H3K79me) induced by DOT1L disruptors is a potential therapeutic target for TNBC clinical management[68-70]. DOT1L-mediated inhibition of H3K79 methylation exhibited anti-tumor activity in TNBC cells and significantly inhibited invasion and migration of TNBC by regulating epithelial mesenchymal transformation (EMT) markers, as well as up-regulation of E-cadherin[71].

SETD2

Histone H3 lysine 36 histone (H3K36) methyltransferase SETD2 is a histone methyltransferase of the nuclear receptor set domain-containing (NSD) family. SETD2 is involved in a variety of cellular processes, including transcriptional regulation, DNA damage repair, and non-histone related functions[72]. Although other enzymes can also mediate monomethylation and dimethylation, SETD2 is the only trimethylase responsible for H3K36. Mutation or loss of function of SETD2 gene can lead to dysfunction of corresponding tumor tissue proteins, leading to tumorigenesis, progression, chemotherapy resistance and poor prognosis, suggesting that SETD2 may be a tumor suppressor[73,74]. SETD2 leads to dysfunction of the corresponding tumor tissue proteins, while SETD2 gene mutations or functional deletions lead to tumorigenesis, progression, chemoresistance, and poor prognosis, suggesting that SETD2 may be a tumor suppressor. one study showed that low level expression SETD2 gastric cancer patients was significantly associated with poor prognosis, and increased expression SETD2 GC cell lines could inhibit cell proliferation, migration and invasion[75]. Therefore SETD2 may be a potential progression in the treatment of gastric cancer..

RIZ1

The retinoblastoma protein-intervening zinc-finger gene 1 (RIZ1) is a methyltransferase gene encoding a SET domain[76]. In cancer research, it is considered as a tumor inhibitor, and its deletion can lead to the development of breast cancer, liver cancer, colorectal cancer, and neuroblastoma[77].Current studies suggest that the most likely mechanism is that RIZ1 can induce G2-M phase cell cycle arrest to inhibit cell proliferation, and at the same time, it can initiate programmed death to promote cell apoptosis[78-80].

PRMT1

PRMT1 is the primary PRMT responsible for 75% of arginine methylation activity in mammalian cells[81]. PRMT1 has received increasing attention due to its important role in the regulation of signal transduction, epigenetic regulation and DNA repair, embryonic development, such as craniofacial morphogenesis and neurodevelopment, as well as diseases such as inflammation and cancer[82]. In an article on heart disease, the blocked translation of PRMT1 resulted in the degradation of Slug and the blocking of the EMT process[83]. This suggests that PRMT1 may be a therapeutic target for some diseases, such as cancer.

PRMT5

PRMT5, a type II PRMT essential for viability and normal development, plays an important role in the control of several key growth and development pathways in humans, and PRMT5 catalyzes symmetric dimethylation of histone H3 arginine 8 (R8) and H4R3 to inhibit the expression of the tumor-suppressor gene 7ST7[84]. For example, in a recent study on gastric cancer, PRMT5 was overexpressed in a large group of human gastric tumors and contributed to the increase of DNA methyltransferase 3A(DNMT3A) to the promoter region of the tumor suppressor gene Iroqois homologous box 1(IRX1) in gastric cancer cells, interacting with the DNA modifying enzyme to promote the occurrence of gastric cancer[85]. It is important to note that although PRMT5 mostly suppresses the transcription of the target gene of action, the histone methylation it induces can also manifest as transcriptional activation. For example, PRMT5 induces H3R8 methylation in the promoter region of adipogenic differentiation genes and promotes its transcription to promote adipogenesis[86]. Unfortunately, the role of PRMT5 in EMT in cancer development is not yet clear and suggests a new line of research.

Other PRMTs

In the PRMT family, except PRMT1 and PRMT5, few studies have been conducted, most of which only explored their structures, and their specific

roles in human growth and development, disease pathology and cancer process have not been clearly explored. These are blind spots in scientific research today, but they may also be the starting point for future scientific research and disease treatment. Of course, in this process, the vast scientific research community needs to contribute its own strength.

Histone demethyltransferases

Histone demmethylases are a class of enzymes that can remove histone methylation, mainly including Lysine specific demethylase(LSD) family and Jumonji domain (JmjC)-containing proteins family[87] .

LSD1

LSD1 (also known as KDM1A, BHC110 and AOF2),as one of the members of favin adenine dinucleotide dependent amine oxidase superfamily, is the frst identifed histone demethylase.Based on its demethylase enzymatic activity targeting both histones and non-histone proteins, it has been increasingly described that LSD1 plays a pivotal role in vast range of cellular processes, such as cell proliferation , epithelial-to-mesenchymal transition (EMT),chromosome segregation , metabolism , stem cell pluripotent regulation and embryonic development etc[88-90].For instance,LSD1 can specifically reduce 4 lysine methylation in histone H3(H3K4) to inhibit Snail - mediated transcription and maintain Snai1 target gene silence state in the invasive cancer cells, thus inhibiting the EMT[91].There is a study suggested that upregulation of LSD1 levels promotes ductal carcinomas in situ (DCIS) to evolve into invasive ductal carcinoma , and also accelerates development, proliferation, and metastasis of breast cancer cells . When exposed to carcinogens, LSD1 will be upregulated and may promote occurrence of early stage breast cancer[92].

JMJC

Most of the methylation and demethylation of histones occur on lysine and arginine residues, and the LSD family is the lysine specific demethylase. Is there any arginine specific demethylase? This is a very important problem in epigenetics that has not been solved[93].Jumonji domain (JmjC)-containing proteins have been characterized as lysine demethylases (KDMs) in a certain degree[94]. Emerging evidences indicate that they also catalyze demethylation reaction on the arginine residues and proteolytic removal of histone tails.If this idea is confirmed further, it will enrich the content of epigenetics and provide a new idea for the treatment of some diseases.The specific mechanism is the use of 2-oxoglutarate (2-OG) and Fe(II) as cofactors through the free radical mechanism of hydroxylated methyl to release formaldehyde. If this idea is confirmed further, it will enrich the content of epigenetics and provide a new idea for the treatment of some diseases. However, due to the very similar structure of JMJC family members and the high homology of its catalytic sites with other 2-OG-dependent oxidases, the research progress of JMJC has been unsatisfactory[95]. Several of the world's leading research companies on protein-modifying enzyme inhibitors have not yet developed JMJC enzyme inhibitors, suggesting that the potential therapeutic impact of such demmethylation enzymes is unclear.KDM6B in EMT: KDM6B (also known as JMJD3) is an α-ketoglutarate dependent demethylase containing a conserved Jumonji C (JmjC) domain. This enzyme is responsible for the demethylation of di- and trimethyllysine 27 (H3K27m2/3) on histone H3 (Table 1). H3K27m2/3 is an epigenetic modification associated with gene silencing . It has been reported that KDM6B expression is higher in metastatic prostate cancer . It is also highly expressed in invasive breast carcinomas compared to normal tissues. Moreover, during TGFβ-induced EMT, TGF-β activates KDM6B which then demethylates H3K27m3 at SNAI1 promoter. This epigenetic modification activates the transcription of SNAI1. This suggests a role for KDM6B during tumor invasion which was demonstrated in MDA-MB-231 cells

Application of methyltransferases and demethylases in therapy

Methylation was previously considered to be an irreversible modification process that stabilizes chromatin regions. With the discovery of demethylase, the mechanism of methylation and demethylating modification has been directed to a more complex domain. However, the emergence of methylase and demethylase inhibitors has directly shifted the focus to clinical applications of methylation and demethylation aimed at exploring and analyzing the underlying strategies for histone methylation.

To date, three PRMT inhibitors have entered clinical trials, including the PRMT5 inhibitors

GSK3326595,JNJ-64619178 and the PRMT1 inhibitor GSK3368715. JNJ64619178 was the first to enter clinical trials of oral nucleoside analogues,which can be used to identify maximum-tolerated dose of a relapse/refractory B cell non-hodgkin's lymphoma or advanced solid tumor in clinical trials on account of its high selectivity, high safety and good efficacy. It can also support clinical trials in patients with lung cancer and other malignancies. The inhibitor GSK3326595 is designed to compete with basal peptides in the treatment of advanced or recurrent solid tumors and non-Hodgkin's lymphoma, with its pharmacodynamics and safety as an initial clinical activity. GSK3368715 is a reversible PRMT inhibitor with anti-tumor effect[(96)].

In addition, several transferase inhibitors have been extended, such as the methyltransferase inhibitor Chaetocin, BIX-01294, DZNEP, and the demethyltransferase inhibitor LSD1 inhibitor (e.g. SL11144). Chaetocin and Bix-01294 had specific inhibitory effects on G9a. Because of the different properties of Chaetocin in high and low concentrations, only the low concentration (2mol/ L) showed a weak inhibitory effect on G9A, and the high concentration (90mol/ L) showed an inhibitory effect on EZH2. BIX-01294 is unique in that it reduces dimethylated H3K9 and has no effect on monomethylated and trimethylated H3K9. DZNEP, a cyclopentanol analogue of 3-azo adenosine, depletes EZH2 to down-regulate H3K27me3 and also down-regulate expression of H3K4me3 related with transcription. It induces apoptosis of breast cancer cells and is harmless to normal cells, but the down-regulation of H3K4me3 makes it not an ideal inhibitor for tumor therapy. LSD1 inhibitors (such as SL11144) are mainly involved in the proliferation of neuroblastoma, which increases H3K4 methylation and reduces cell growth[(97)].

Most studies have shown that histone methylation promotes tumor development while demethylation inhibits tumor development. In the research process, some methylase inhibition and demethylase promotion were also found, and even some enzymes had special recognition and had "selection awareness" in different situations.For example, RBP2, a histone demethylase, is upregulated to promote EMT and inhibit cancer cell senescence, and is overexpressed in human gastric cancer cells and lung cancer tissues. JMJD6 is similar to RBP2, and the expression level of JMJD6 is highest when the survival time is short, and it is overexpressed in cancer cells, especially colon cancer cells.Moreover, SET8 showed dual functions in breast cancer samples, that is, the expression of SET8 was positively correlated with metastasis and N-cadherin, and negatively correlated with E-cadherin. Specifically, SET8 and TWIST interact with CDH1, inhibit CDH1 gene expression, downregulate E-cadherin, induce epithelial-mesenchymal transition, and thereby increase breast cancer cell metastasis. In addition, the downregulation of LSD1 promotes tumor metastasis and poor prognosis in Snail mediated E-cadherin silencing. In breast cancer studies, LSD1 inhibited the expression of TGF-1 and inhibited cancer metastasis[(98-101)].

Although many enzyme inhibitors have been expanded into research, the drugs being put into the clinic still need to be watched. Moreover, enzymes with dual effects, such as SET8 and LSD1, need to be further explored and studied, which is of great significance for the progress of tumor therapy.

Summary and Outlook

According to incomplete statistics, about 10 million people die of cancer every year, and this number is still increasing every year. Therefore, it is very necessary to study the causes, mechanisms and treatment of cancer. In fact, cancer related research has been carried out all the time, but no substantive breakthrough has been made.The main reason is that cancer cells themselves are prone to mutation, which makes it difficult for us to find targets. However, according to previous studies, most cancers occur in EMT, and these common areas can give us some ideas for treatment.

It is regulated by epigenetics during the occurrence of EMT in cancer cells, among which histone modification is the most complex epigenetic regulation mode which may also have the most research potential. At present, histone methylation has been studied more clearly than others in histone modification. In this review, some mechanisms and functions of histone methylation in cancer EMT process and its potential for cancer treatment are reviewed.

Histone methylation and demethylation is realized by methyltransferases and demethylases. These emzymes can have different effects depending on their action sites, such as influencing hormone secretion, regulating lipid metabolism, and even controlling cell cycle, etc. More importantly, histone methylation plays a crucial role in the

genesis and development of tumors. It can directly or indirectly act on epithelial markers of EMT, leading to its overexpression or inhibition, and ultimately inducing cancer metastasis and invasion. In general, histone methyltransferases are shown to promote cancer progression, while histone demethylases inhibit cancer development. Therefore, down-regulation of histone methyltransferase expression and demethylase can be used as a new entry point for cancer treatment.

Although histone methylation and demethylation modification during epithelial stromal transformation open new doors to the treatment of tumors, the role of many histone modifiers in tumors remains controversial. Whether histone modifiers are drivers or inhibitors of tumor genesis mainly depends on the type of histone modifiers and their expression patterns in tumors.

On this basis, future research strategies should be implemented to clinical trials and use of histone methylation related modifiers with definite efficacy, critical research and efficacy determination of controversial histone methylation related modifiers, and in-depth exploration of some research blind spots.

Conflicts of Interest

The authors declare no competing interests.

References

1. Fu, L., Mou, J., Deng, Y., Ren, X. and Qiu, S., Front. Chem., 2022, 10, 940427.
2. Rašić, I., Rašić, A., Akšamija, G. and Radović, S., Acta Clin. Croat., 2018, 57, 411–416.
3. Xu, J., Chen, J., Zhang, X., Zhang, Z. and Wang, G., Sci. Rep., 2025, 15, 44699.
4. Cammarota, F., Conte, A., Aversano, A., Muto, P., Ametrano, G., Riccio, P., Turano, M., Valente, V., Delrio, P., Izzo, P., Pierantoni, G. M. and De Rosa, M., Mol. Med. Rep., 2020, 21, 1501–1508.
5. Ahrens, T. D., Bang-Christensen, S. R., Jørgensen, A. M., Løppke, C., Spliid, C. B., Sand, N. T., Clausen, T. M., Salanti, A. and Agerbæk, M. Ø., Front. Cell Dev. Biol., 2020, 8, 749.
6. Liu, B., Du, R., Zhou, L., Xu, J., Chen, S., Chen, J., Yang, X., Liu, D. X., Shao, Z. M., Zhang, L., Yu, Z., Xie, N., Guan, J. L. and Liu, S., Theranostics, 2018, 8, 5801–5813.
7. Chen, J., Wu, S., Peng, Y., Zhao, Y., Dong, Y., Ran, F., Geng, H., Zhang, K., Li, J., Huang, S. and Wang, Z., Front. Pharmacol., 2023, 14, 1200017.
8. Chen, C., Peng, R., Jin, S., Tang, Y., Liu, H., Tu, D., Su, B., Wang, S., Jiang, G., Cao, J., Zhang, C. and Bai, D., Discov. Oncol., 2024, 15, 808.
9. Cárdenas, S., Colombero, C., Panelo, L., Dakarapu, R., Falck, J. R., Costas, M. A. and Nowicki, S., Biochim. Biophys. Acta Mol. Cell Biol. Lipids, 2020, 1865, 158573.
10. Lamouille, S., Xu, J. and Derynck, R., Nat. Rev. Mol. Cell Biol., 2014, 15, 178–196.
11. Xia, C., Wang, Y., Liu, C., Wang, L., Gao, X., Li, D., Qi, W., An, R. and Xu, H., Molecules, 2020, 25, 451.
12. Kalluri, R. and Weinberg, R. A., J. Clin. Invest., 2009, 119, 1420–1428.
13. Qin, S., Xie, B., Wang, Q., Yang, R., Sun, J., Hu, C., Liu, S., Tao, Y. and Xiao, D., MedComm, 2024, 5, e551.
14. Si, T. E., Li, Z., Zhang, J., Su, S., Liu, Y., Chen, S., Peng, G. H., Cao, J. and Zang, W., Front. Cell Dev. Biol., 2023, 11, 1157893.
15. Bedi, U., Mishra, V. K., Wasilewski, D., Scheel, C. and Johnsen, S. A., Oncotarget, 2014, 5, 2016–2029.
16. Kiesslich, T., Pichler, M. and Neureiter, D., Mol. Clin. Oncol., 2013, 1, 3–11.
17. Lin, Y., Wu, Y., Li, J., Dong, C., Ye, X., Chi, Y. I., Evers, B. M. and Zhou, B. P., EMBO J., 2010, 29, 1803–1816.
18. Dong, C., Wu, Y., Yao, J., Wang, Y., Yu, Y., Rychahou, P. G., Evers, B. M. and Zhou, B. P., J. Clin. Invest., 2012, 122, 1469–1486.
19. Yang, F., Sun, L., Li, Q., Han, X., Lei, L., Zhang, H. and Shang, Y., EMBO J., 2012, 31, 110–123.
20. Kornberg, R. D. and Lorch, Y., Cell, 1999, 98, 285–294.
21. Fischle, W., Wang, Y. and Allis, C. D., Curr. Opin. Cell Biol., 2003, 15, 172–183.
22. Zaib, S., Rana, N. and Khan, I., Curr. Med. Chem., 2022, 29, 2399–2411.
23. Cho, M. H., Park, J. H., Choi, H. J., Park, M. K., Won, H. Y., Park, Y. J., Lee, C. H., Oh, S. H., Song, Y. S., Kim, H. S., Oh, Y. H., Lee, J. Y. and Kong, G., Nat. Commun., 2015, 6, 7821.
24. Choi, H. J., Park, J. H., Park, M., Won, H. Y., Joo, H. S., Lee, C. H., Lee, J. Y. and Kong, G., EMBO Rep., 2015, 16, 1288–1298.
25. Wang, X. and Zhu, W. G., Ai Zheng, 2008, 27, 1018–1025.
26. Schübeler, D., MacAlpine, D. M., Scalzo, D.,

Wirbelauer, C., Kooperberg, C., van Leeuwen, F., Gottschling, D. E., O'Neill, L. P., Turner, B. M., Delrow, J., Bell, S. P. and Groudine, M., Genes Dev., 2004, 18, 1263–1271.
27. Liang, G., Lin, J. C., Wei, V., Yoo, C., Cheng, J. C., Nguyen, C. T., Weisenberger, D. J., Egger, G., Takai, D., Gonzales, F. A. and Jones, P. A., Proc. Natl. Acad. Sci. U.S.A., 2004, 101, 7357–7362.
28. McDonald, O. G., Wu, H., Timp, W., Doi, A. and Feinberg, A. P., Nat. Struct. Mol. Biol., 2011, 18, 867–874.
29. Yang, W., Zheng, Y., Chen, S., Guo, J., Pan, Z. and Yu, Y., Int. J. Mol. Med., 2025, 56, 216.
30. Li, N. N., Lun, D. X., Gong, N., Meng, G., Du, X. Y., Wang, H., Bao, X., Li, X. Y., Song, J. W., Hu, K., Li, L., Li, S. Y., Liu, W., Zhu, W., Zhang, Y., Li, J., Yao, T., Mou, L., Han, X., Hao, F., Hu, Y., Liu, L., Zhu, H., Wu, Y. and Liu, B., J. Pharm. Anal., 2024, 14, 100905.
31. Benevolenskaya, E. V., Biochem. Cell Biol., 2007, 85, 435–443.
32. Lu, T. and Stark, G. R., Cancer Res., 2015, 75, 3692–3695.
33. Klose, R. J., Kallin, E. M. and Zhang, Y., Nat. Rev. Genet., 2006, 7, 715–727.
34. Chakraborty, R., Borah, P., Dutta, P. P. and Sen, S., World J. Diabetes, 2022, 13, 696–716.
35. Lee, J. Y. and Kong, G., Cell. Mol. Life Sci., 2016, 73, 4643–4660.
36. Hua, C., Chen, J., Li, S., Zhou, J., Fu, J., Sun, W. and Wang, W., Front. Oncol., 2021, 11, 779918.
37. Ren, B. J., Zhou, Z. W., Zhu, D. J., Ju, Y. L., Wu, J. H., Ouyang, M. Z., Chen, X. W. and Zhou, S. F., Int. J. Mol. Sci., 2015, 17, 41.
38. Wang, G., Zhang, Z. J., Jian, W. G., Liu, P. H., Xue, W., Wang, T. D., Meng, Y. Y., Yuan, C., Li, H. M., Yu, Y. P., Liu, Z. X., Wu, Q., Zhang, D. M. and Zhang, C., Mol. Cancer, 2019, 18, 15.
39. Jiao, P., Wang, X. P., Luoreng, Z. M., Yang, J., Jia, L., Ma, Y. and Wei, D. W., Int. J. Biol. Sci., 2021, 17, 2308–2322.
40. Shi, S., Wang, B., Wan, J., Song, L., Zhu, G., Du, J., Ye, L., Zhao, Q., Cai, J., Chen, Q., Xiao, K., He, J., Yu, L. and Dai, Z., Acta Biochim. Biophys. Sin., 2022, 54, 1008–1020.
41. Zhang, C., Wang, Z., Ji, Q. and Li, Q., Oncotarget, 2017, 8, 91723–91733.
42. An, J., Xu, J., Li, J., Jia, S., Li, X., Lu, Y., Yang, Y., Lin, Z., Xin, X., Wu, M., Zheng, Q., Pu, H., Gui, X., Li, T. and Lu, D., Oncotarget, 2017, 8, 49093–49109.
43. Eldehna, W. M., Al-Rashood, S. T., Al-Warhi, T., Eskandrani, R. O., Alharbi, A. and El Kerdawy, A. M., J. Enzyme Inhib. Med. Chem., 2021, 36, 270–285.
44. Yang, C., Zhang, J., Ma, Y., Wu, C., Cui, W. and Wang, L., J. Exp. Clin. Cancer Res., 2020, 39, 173.
45. Morera, L., Lübbert, M. and Jung, M., Clin. Epigenetics, 2016, 8, 57.
46. Min, J., Feng, Q., Li, Z., Zhang, Y. and Xu, R. M., Cell, 2003, 112, 711–723.
47. Nguyen, A. T. and Zhang, Y., Genes Dev., 2011, 25, 1345–1358.
48. Lafont, J. E., Moustaghfir, S., Durand, A. L. and Mallein-Gerin, F., Front. Physiol., 2023, 14, 1070241.
49. Li, J., Zhao, Z., Carter, C., Ehrlich, L. I., Bedford, M. T. and Richie, E. R., J. Immunol., 2013, 190, 597–604.
50. Tang, Y., Meng, X., Luo, X., Yao, W., Tian, L., Zhang, Z., Zhao, Y., Xiao, J., Zhu, H. and Hu, J., Cell Death Discov., 2024, 10, 477.
51. Yin, S., Liu, L., Ball, L. E., Wang, Y., Bedford, M. T., Duncan, S. A., Wang, H. and Gan, W., Cell Rep., 2023, 42, 112316.
52. Zhao, Y., Lu, Q., Li, C., Wang, X., Jiang, L., Huang, L., Wang, C. and Chen, H., Cell Death Dis., 2019, 10, 359.
53. Abe, Y. and Tanaka, N., Cells, 2020, 9, 1973.
54. Brekker, M. A., Sartawi, T., Sawatzky, T. M., Causey, C. P., Rehman, F. K. and Knuckley, B., J. Biol. Chem., 2022, 298, 102205.
55. Simon, J. A. and Lange, C. A., Mutat. Res., 2008, 647, 21–29.
56. Pandey, S., Simmons, G. E. Jr., Malyarchuk, S., Calhoun, T. N. and Pruitt, K., Genes Cancer, 2015, 6, 408–421.
57. Zheng, M., Cao, M. X., Luo, X. J., Li, L., Wang, K., Wang, S. S., Wang, H. F., Tang, Y. J., Tang, Y. L. and Liang, X. H., J. Cell. Mol. Med., 2019, 23, 6942–6954.
58. Inazumi, H. and Kuwahara, K., Biology, 2022, 11, 1197.
59. Mayr, C., Helm, K., Jakab, M., Ritter, M., Shrestha, R., Makaju, R., Wagner, A., Pichler, M., Beyreis, M., Staettner, S., Jaeger, T., Klieser, E., Kiesslich, T. and Neureiter, D., Hum. Pathol., 2018, 72, 117–126.
60. Casciello, F., Windloch, K., Gannon, F. and Lee, J. S., Front. Immunol., 2015, 6, 487.
61. Mitra, A., Mishra, L. and Li, S., Oncotarget,

2015, 6, 10697–10711.
62. Lin, Y., Dong, C. and Zhou, B. P., Curr. Pharm. Des., 2014, 20, 1698–1705.
63. Tachibana, M., Sugimoto, K., Nozaki, M., Ueda, J., Ohta, T., Ohki, M., Fukuda, M., Takeda, N., Niida, H., Kato, H. and Shinkai, Y., Genes Dev., 2002, 16, 1779–1791.
64. Dong, C., Wu, Y., Yao, J., Wang, Y., Yu, Y., Rychahou, P. G., Evers, B. M. and Zhou, B. P., J. Clin. Invest., 2012, 122, 1469–1486.
65. Serrano-Gomez, S. J., Maziveyi, M. and Alahari, S. K., Mol. Cancer, 2016, 15, 18.
66. Dong, C., Wu, Y., Wang, Y., Wang, C., Kang, T., Rychahou, P. G., Chi, Y. I., Evers, B. M. and Zhou, B. P., Oncogene, 2013, 32, 1351–1362.
67. Kurani, H. and Slingerland, J. M., Cancer Res., 2025, 85, 838–847.
68. Liu, L., Zou, J., Guan, Y., Zhang, Y., Zhang, W., Zhou, X., Xiong, C., Tolbert, E., Zhao, T. C., Bayliss, G. and Zhuang, S., FASEB J., 2019, 33, 11941–11958.
69. Jones, B., Su, H., Bhat, A., Lei, H., Bajko, J., Hevi, S., Baltus, G. A., Kadam, S., Zhai, H., Valdez, R., Gonzalo, S., Zhang, Y., Li, E. and Chen, T., PLoS Genet., 2008, 4, e1000190.
70. Nguyen, A. T. and Zhang, Y., Genes Dev., 2011, 25, 1345–1358.
71. Byun, W. S., Lee, G. H., Park, H. G. and Lee, S. K., Pharmaceuticals, 2020, 14, 18.
72. Feoli, A., Viviano, M., Cipriano, A., Milite, C., Castellano, S. and Sbardella, G., RSC Chem. Biol., 2021, 3, 359–406.
73. Fahey, C. C. and Davis, I. J., Cold Spring Harb. Perspect. Med., 2017, 7, a026468.
74. Chen, R., Zhao, W. Q., Fang, C., Yang, X. and Ji, M., J. Cancer, 2020, 11, 3349–3356.
75. Chen, Z., Raghoonundun, C., Chen, W., Zhang, Y., Tang, W., Fan, X. and Shi, X., Biochem. Biophys. Res. Commun., 2018, 498, 579–585.
76. Liu, Z. Y., Wang, J. Y., Liu, H. H., Ma, X. M., Wang, C. L., Zhang, X. P., Tao, Y. Q., Lu, Y. C., Liao, J. C. and Hu, G. H., Oncogene, 2013, 32, 1216–1222.
77. Huang, S., Shao, G. and Liu, L., J. Biol. Chem., 1998, 273, 15933–15939.
78. Chadwick, R. B., Jiang, G. L., Bennington, G. A., Yuan, B., Johnson, C. K., Stevens, M. W., Niemann, T. H., Peltomaki, P., Huang, S. and de la Chapelle, A., Proc. Natl. Acad. Sci. U.S.A., 2000, 97, 2662–2667.
79. Jiang, G. L., Liu, L., Buyse, I. M., Simon, D. and Huang, S., Int. J. Cancer, 1999, 83, 541–546.
80. Zhang, C., Zhu, Q., He, H., Jiang, L., Qiang, Q., Hu, L., Hu, G., Jiang, Y., Ding, X. and Lu, Y., BMC Cancer, 2015, 15, 990.
81. Zhou, X., Chen, H., Li, J., Shi, Y., Zhuang, S. and Liu, N., Front. Pharmacol., 2022, 13, 885527.
82. Bedford, M. T. and Clarke, S. G., Mol. Cell, 2009, 33, 1–13.
83. Gou, Y., Li, J., Jackson-Weaver, O., Wu, J., Zhang, T., Gupta, R., Cho, I., Ho, T. V., Chen, Y., Li, M., Richard, S., Wang, J., Chai, Y. and Xu, J., J. Dent. Res., 2018, 97, 1510–1518.
84. Shailesh, H., Zakaria, Z. Z., Baiocchi, R. and Sif, S., Oncotarget, 2018, 9, 36705–36718.
85. Liu, X., Zhang, J., Liu, L., Jiang, Y., Ji, J., Yan, R., Zhu, Z. and Yu, Y., Biochim. Biophys. Acta Mol. Basis Dis., 2018, 1864, 2835–2844.
86. Paul, C., Sardet, C. and Fabbrizio, E., Biol. Open, 2015, 4, 312–316.
87. Pippa, S., Mannironi, C., Licursi, V., Bombardi, L., Colotti, G., Cundari, E., Mollica, A., Coluccia, A., Naccarato, V., La Regina, G., Silvestri, R. and Negri, R., Molecules, 2019, 24, 1739.
88. Lan, F., Nottke, A. C. and Shi, Y., Curr. Opin. Cell Biol., 2008, 20, 316–325.
89. Lv, S., Bu, W., Jiao, H., Liu, B., Zhu, L., Zhao, H., Liao, J., Li, J. and Xu, X., Eur. J. Cell Biol., 2010, 89, 557–563.
90. Whyte, W. A., Bilodeau, S., Orlando, D. A., Hoke, H. A., Frampton, G. M., Foster, C. T., Cowley, S. M. and Young, R. A., Nature, 2012, 482, 221–225.
91. Lin, T., Ponn, A., Hu, X., Law, B. K. and Lu, J., Oncogene, 2010, 29, 4896–4904.
92. Yang, G. J., Lei, P. M., Wong, S. Y., Ma, D. L. and Leung, C. H., Molecules, 2018, 23, 3194.
93. Meng, Y., Li, H., Liu, C., Zheng, L. and Shen, B., J. Mol. Cell Biol., 2018, 10, 371–373.
94. Klose, R. J., Kallin, E. M. and Zhang, Y., Nat. Rev. Genet., 2006, 7, 715–727.
95. McCabe, M. T., Mohammad, H. P., Barbash, O. and Kruger, R. G., Cancer J., 2017, 23, 292–301.
96. Li, X., Wang, C., Jiang, H. and Luo, C., Expert Opin. Ther. Pat., 2019, 29, 97–114.
97. Gu, Y., Zhang, X., Yu, W. and Dong, W., J. Cancer, 2022, 13, 623–640.
98. Teng, Y. C., Lee, C. F., Li, Y. S., Chen, Y. R., Hsiao, P. W., Chan, M. Y., Lin, F. M., Huang, H. D., Chen, Y. T., Jeng, Y. M., Hsu, C. H., Yan,

Q., Tsai, M. D. and Juan, L. J., Cancer Res., 2013, 73, 4711–4721.
99. Wu, J., Qiao, K., Du, Y., Zhang, X., Cheng, H., Peng, L. and Guo, Z., Sci. Rep., 2020, 10, 4490.
100. Yang, F., Sun, L., Li, Q., Han, X., Lei, L., Zhang, H. and Shang, Y., EMBO J., 2012, 31, 110 123.
101. Serrano-Gomez, S. J., Maziveyi, M. and Alahari, S. K., Mol. Cancer, 2016, 15, 18.