

# Epigenetic modification regulates tumor progression and metastasis through EMT (Review)

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**Abstract.** Epigenetics is the study of heritable molecular determinants that are independent of phenotypic features. The epigenetic features include DNA methylation, histone modifications, non-coding RNAs, and chromatin remodeling. In multicellular organisms, the epigenetic state of a cell is critical in determining its differentiation status and its ability to perform its proper function. These processes are now well recognized as being a substantial factor in tumor progression and metastasis. The process through which epithelial cells acquire mesenchymal features is known as epithelial-mesenchymal transition (EMT). EMT is associated with tumorigenesis, invasion, metastasis, and resistance to therapy in cancer. In the present review, we examine the recent studies that demonstrate the biological role of epigenetics, in particular, DNA methylation, histone modifications, non-coding RNAs, and chromatin remodeling in tumor progression and metastasis by regulating EMT status, and we provide an overview of the current state of knowledge regarding the epigenetics involvement in tumor progression and metastasis. Because epigenetic changes can be reversed, learning more about their biological roles in EMT will not only help us better understand how cancer progresses and spreads, but it will also help us identify new ways to

diagnose and treat human malignancy, which is currently lacking in the clinical setting.

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## 1. Introduction

Metastasis remains the leading cause of mortality in cancer patients, despite recent advancements in the diagnosis and treatment of a variety of cancers. It becomes more and more heterogeneous as cancer progresses, resulting in the production of aggressive subsets of cancer cells that invade local tissues, lymph vessels, and circulatory systems before spreading throughout the body. This aggressive behavior of the original tumor eventually results in the extensive spread and metastasis of the primary tumor. Therefore, understanding the mechanism of cancer metastasis is an important step in determining therapeutic targets that can be used to slow or stop cancer growth and progression (1). The process of cell transformation and cancer progression includes gene mutations and epigenetic changes and the rewiring of cell signals, and the reprogramming of metabolic pathways. Furthermore, a vast body of literature published over the past few decades has shown that epigenetic modifications are implicated in the formation and progression of the tumor. It has also been said that genetic and epigenetic changes are closely linked during the development of tumors (2).

Epigenetic mechanisms of tumor cell growth and gene expression regulation include DNA methylation, covalent histone modifications, glycosylation, and ubiquitination. These epigenetic modifications exhibit unique features and distribution patterns in different tumor cells. The unique pattern of combinations of these modifications, collectively referred to as the epigenome, is a critical determinant of cell fate and gene activity (3). Collectively, the epigenetic state within cells is

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tightly controlled to maintain an appropriate state of differentiation. In cancer, this fine-tuned genomic programming is disrupted, resulting in unregulated cell proliferation, defective differentiation, and resistance to apoptosis (4). Epigenetic events, most notable stability of gene expression and genetic modifications, are not attributed to any changes in the primary DNA sequence. Here, we examine the current findings into the contribution of epigenetics to metastasis, which may guide cell dissemination from the primary tumor or eventual growth and colonization at distant sites. This information will allow us to uncover the functional importance of these epigenetic phenomena and provide informative therapeutic value for cancers targeting epigenetic changes in metastatic cells.

## 2. Process of cancer metastasis

Metastasis represents a major obstacle in cancer treatment and is the leading cause of cancer-related deaths. The process from primary local tumor to distant metastasis is divided into 6 steps: i) local invasion, ii) intravasation, iii) survival in the circulation, iv) arrest at the distant organ site and extravasation, v) micrometastasis formation, and vi) metastatic colonization (Fig. 1) (5). In order to pass these steps, different molecular pathways have been shown to be important, including mitogen-activated protein kinase (MAPK), phosphatidylinositol 3 kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR), hepatocyte growth factor (HGF)/mesenchymal-epithelial transition tyrosine kinase receptor (Met), Wnt/ $\beta$ -catenin, and vascular endothelial growth factor (VEGF) signal transduction (6). Furthermore, some cytokines secreted by macrophages can lead to the loss of vascular connections and increase the permeability of blood vessels when tumor cells invade blood vessels. Various cellular components in blood vessels will kill circulating tumor cells, whereas circulating tumor cells can recruit platelets to resist killing (7).

Cancer cells break away from the original site and infiltrate the surrounding normal tissues. Morphologically, the cancer cell transitions from a highly differentiated to an undifferentiated state (5). Cancer cells undergo mesenchymal-epithelial transition (EMT) during migration and invasion. EMT is a cellular process in which cells lose their epithelial features and acquire mesenchymal ones (8). The loss of E-cadherin and its inhibition or attenuation of cell adhesion during EMT are considered to be a critical step. E-cadherin is a type of  $\text{Ca}^{2+}$ -dependent intercellular adhesion molecule in epithelial tissues. E-cadherin is a single-channel transmembrane glycoprotein containing five extracellular repeats that mediate  $\text{Ca}^{2+}$ -dependent interactions with opposing molecules on adjacent cells (9). Expression or the cell surface localization of E-cadherin is frequently lost in advanced tumors and is associated, at least in some cases, with the incidence of metastasis and tumor recurrence (10). Loss of E-cadherin expression in human tumors is most commonly caused by methylation of its promoter, or upregulation of the transcriptional repressors SNAIL, SIP1 and zinc finger E-box-binding homeobox 1 (ZEB1), which target the E-cadherin promoter (11). Loss of E-cadherin function is a cause of promotion of invasion and metastasis, primarily through the transformation of epithelial tumor cells into highly migratory and invasive cells (12).

It can combine with  $\beta$ -catenin in the cytoplasm to form a complex. This complex can be directly connected to the actin cytoskeleton to maintain the stability of cell adhesion and cell polarity (13). If the expression of E-cadherin is blocked, tumor growth factor (TGF)- $\beta$ , Wnt/ $\beta$ -catenin, Hedgehog, Notch, and tumor necrosis factor (TNF) signals will induce cancer cell EMT via Twist/Snail/Slug/ZEB1, causing cancer cells to invade and metastasize (8,14).

For intravasation, the migration of cancer cells to blood vessels is caused by factors involved in local invasion—the secretion of proteases such as matrix metalloproteinase (MMP)-1, -2, and -9 and the activation of the urokinase-type plasminogen activator (uPA)/uPA receptor (uPAR) (15). Cancer cells mainly invade capillaries and venules, and large blood vessels are resistant to tumor cell invasion. Tissue fibrosis is also resistant to cancer cell invasion. Cirrhotic organs are not prone to metastasis, and myofibroblasts from cirrhosis can secrete MMP inhibitors (TIMP). In addition, the heart and skeletal muscles are also resistant to metastasis (16).

After cancer cells enter the circulation, they are prone to anoikis due to their lack of support from the extracellular matrix (ECM) (17). It is estimated that less than 1% of circulating tumor cells (CTCs) that circulate in the blood on a daily basis would survive and have a possibility of spreading to produce distant metastases (18). When cancer cells are in circulation, they are attacked by immune cells, which in turn are assaulted by cancer cells. In order to prevent immune cells from attacking cancer cells, fibrin and platelets adhere to the surface of cancer cells (19). Less than 1% of cancer cells found in the blood have a chance of surviving, and some cancer cells are in a dormant state, and less than 0.01% of cells with high metastatic potential can emerge from blood vessels to form metastases (20).

The following are the leading causes of cancer cells to stop growing. i) Cancer cells are prevented from spreading by capillary stenosis. Then the cancer cells extravasate through the endothelial cells and exit the blood vessels to establish metastases. ii) The cancer cell surface protein interacts with the microvascular endothelial surface (21). The detailed mechanism of cancer cell metastasis to the organs is currently unclear, which may be related to organ microvascular endothelial cells. Studies have shown that cancer cells only adhere to microvascular endothelial cells, not large vascular endothelial cells (22). There are some specific molecules in organ microvascular endothelial cells. These molecules include adhesion molecules, intercellular adhesion molecule-1 (ICAM-1), selectin and integrin (23), and endothelial cells secrete chemo-attractants [CXC chemokine receptor 4 (CXCR4), CXC chemokine receptor 12 (CXCR12), and chemokine (C-C motif) receptor 1 (CCR1)] (24). Therefore, the specific molecules may be the main reason for cancer cell arrest. The specificity of metastatic sites for each tumor entity is also called tissue tropism (25). Tissue tropism helps predict the future metastatic site through these specific molecules and may become the target of future anti-metastatic drug therapy (26).

After cell extravasation, CTCs need to create specific conditions to reach the target organs (27). The steps of cancer cells exiting the vessel wall are opposite to the direction of their entering the vessel wall (28). Cancer cells removed from blood vessels are in an unfavorable environment, and

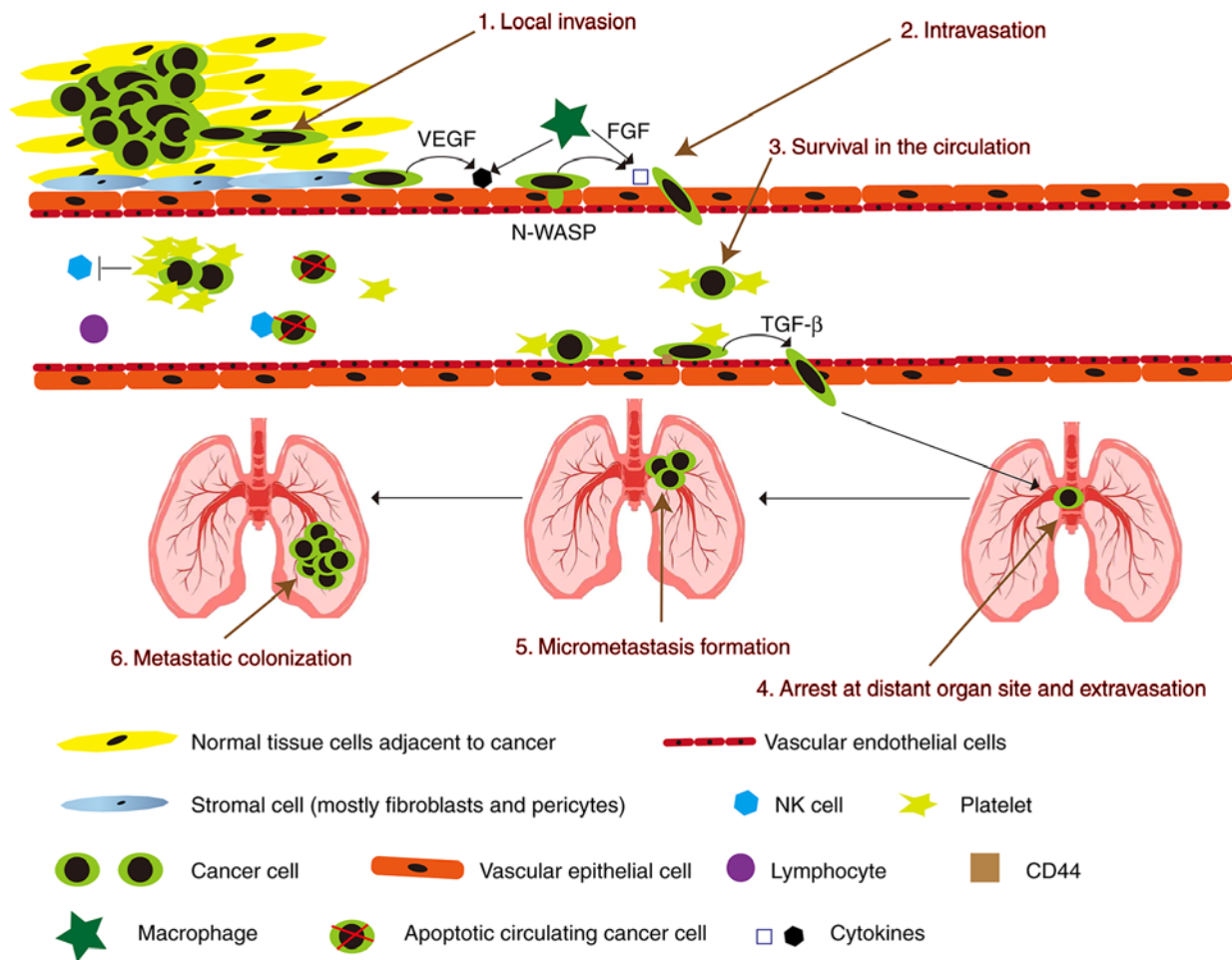


Figure 1. Schematic diagram showing the invasion-metastasis cascade. VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; N-WASP, neural Wiskott-Aldrich syndrome protein; TGF- $\beta$ , transforming growth factor- $\beta$ ; NK, natural killer.

they have to overcome various difficulties to establish metastases (29). Primary cancer cells release growth factors into the circulation (30). These growth factors lead to an upregulation of vascular endothelial growth factor (VEGF)-A, placental growth factor (PlGF), transforming growth factor- $\beta$  (TGF- $\beta$ ), and inflammatory proteins S100A8/9 at the future metastatic sites (31). From the results, the cells that can establish metastases should have the properties of cancer stem cells (32).

As the final step of the metastatic cascade, micro-metastases have now spread to distant organs. In specific niches or in undefined spots, a plethora of genes and signals support metastatic cell growth and survival (33). Many of these pro-metastatic stromal mediators ultimately activate stem cell support pathways (Wnt, TGF- $\beta$ , BMP, Notch, Stat3), positional and mechanical pathways (Hedgehog, Hippo), pathways that integrate cell metabolism and survival (PI3K/AKT, MAPK, HIF), and inflammatory pathways (NF- $\kappa$ B, Stat1) (34). Cancer kills the most individuals when it spreads to other parts of the body. Preventing the formation of new niches may be a new way to treat metastatic diseases.

### 3. Epigenetic in tumor progression and metastasis

Epigenetic research aims to reveal how the environment, social status, psychosocial factors, and nutrition influence

the expression of an individual's genetic information (35). Epigenetics is responsible for initiating and maintaining epigenetic silencing and regulating gene expression profiles and is the cornerstone of a range of cellular processes, including cell differentiation, gene expression, X chromosome inactivation, embryogenesis, and genomic imprinting (36). In addition, epigenetics also plays a significant role in the regulation of tumor metastasis. We will illustrate the impact of epigenetics on tumor metastasis from the following aspects (Fig. 2).

*Metastasis is regulated by DNA methylation.* DNA methylation is an epigenetic modification first discovered in humans in the early 1980's and the most intensely studied in epigenetic regulatory mechanisms (37,38). In a broad sense, DNA methylation refers to the chemical modification process in which a specific base in the DNA sequence obtains a methyl group by covalent bonding with S-adenosyl methionine (SAM) as a methyl donor under the catalysis of DNA methyltransferase (DNMT). This DNA methylation modification can occur at the C-5 position of cytosine, the N-6 position of adenine, and the G-7 position of guanine (39). In general, DNA methylation mainly refers to the methylation process that occurs at the 5th carbon atom on cytosine in CpG dinucleotides, and the product is called 5-methylcytosine (5-mC), which is the main

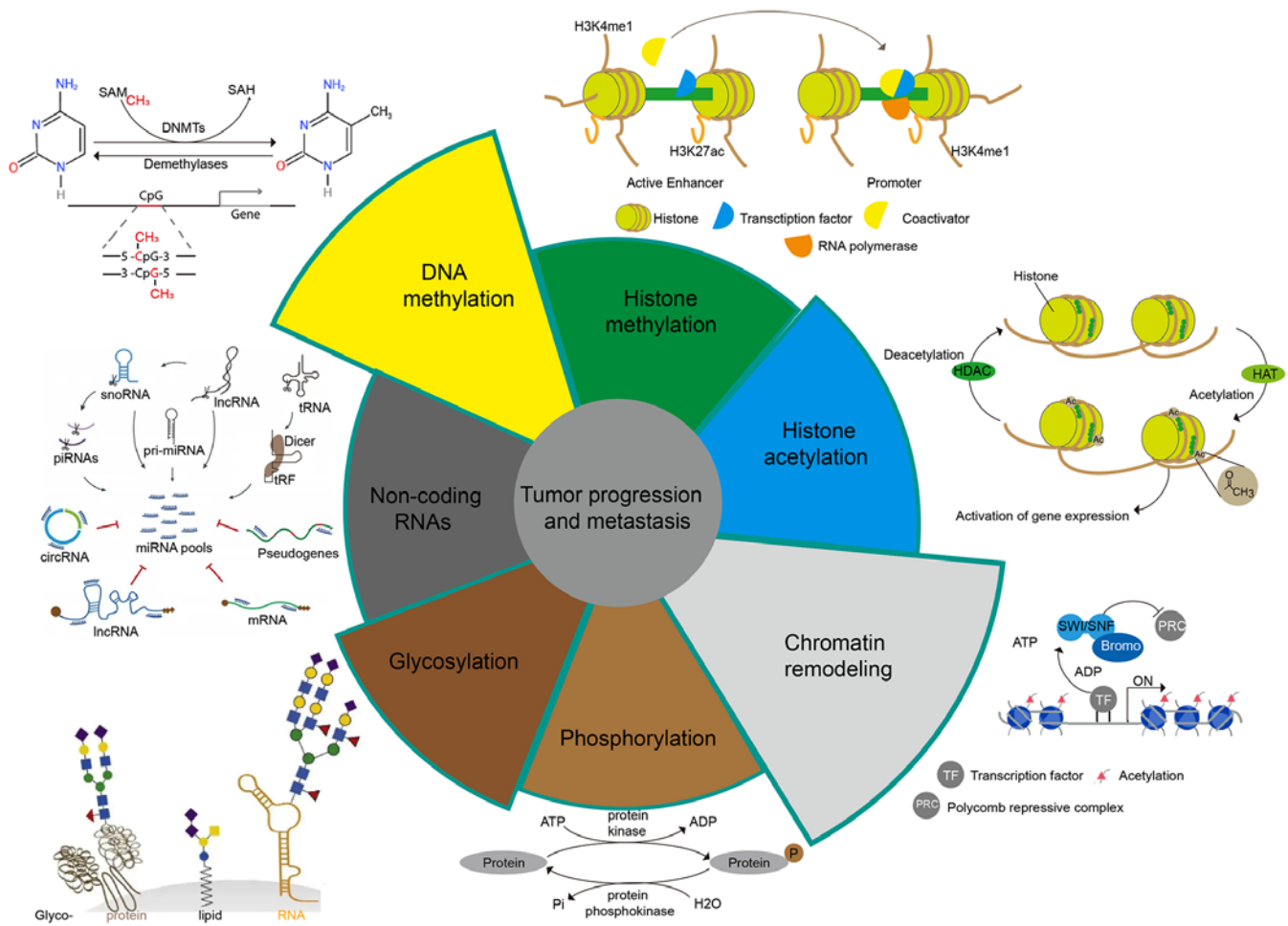


Figure 2. Epigenetic types of tumor metastasis. DNMTs, DNA methyltransferases; snoRNA, small nucleolar RNA; lncRNA, long non-coding RNA; piRNAs, piwi-interacting RNAs; circRNA, circular RNA; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; SWI/SNF, switching defective/sucrose non-fermenting; Bromo, bromodomain.

form of DNA methylation in eukaryotes such as plants and animals, and the only form of DNA methylation in mammals found (40). DNA methylation plays an important role in regulating individual growth, development, gene expression patterns, and genome stability without changing the DNA sequence, and this modification is stable during development and cell proliferation. A large number of studies in recent years have shown that DNA aberrant methylation is closely related to the occurrence, development, and carcinogenesis of tumors (41,42).

The DNA methyltransferase (DNMT) family consists of a group of conserved DNA-modifying enzymes that play central roles in epigenetic regulation. Five DNMT family members have been found in mammals: DNMT1, DNMT2, DNMT3a, DNMT3b, and DNMT3L (43). However, only DNMT1, DNMT3a, and DNMT3b interact to generate the overall cytosine methylation pattern. These independently encoded proteins are divided into generating DNA methylases (DNMT3a and DNMT3b) and maintaining DNA methylases (DNMT1). DNMT2 and DNMT3L are not considered cytosine methyltransferases (44). DNMT3L, on the other hand, has been shown to stimulate *de novo* DNA methylation via DNMT3a and to mediate transcriptional repression via interaction with histone deacetylase 1 (45).

The role of DNA methylation in tumors is mainly manifested in the following aspects. First, cytosine in methylated CpG island dinucleotides is deaminated to thymine at a high frequency, causing gene mutation (46). Second, tumor-suppressor genes and DNA repair genes are silenced due to hypermethylation (47). Third, oncogene methylation levels are reduced and activated (48); and fourth, the overall reduction in methylation levels of the genome causes transposons and repetitive sequences to activate, resulting in decreased chromosomal stability (49). These factors are important reasons for the development, metastasis, and progression of tumors, which eventually lead to the death of patients. The overall DNA methylation level (i.e., methylation profile) and changes in the degree of methylation of specific genes can be used as tumor diagnostic indicators (50).

In normal cells, heterochromatin is hypermethylated around the central point; however, in many tumors, this mechanism is disrupted, and DNA methylation in normally inactive regions is lost. Transposable elements are subsequently reactivated and can integrate at arbitrary sites in the genome, leading to mutation and genomic instability (51). Therefore, DNA methylation plays a vital role in tumor progression and metastasis. DNMT1 is a maintenance methyltransferase that methylates cytosines in hemimethylated CpG dinucleotides (52). DNMT1

is required for the maintenance of trimethylation of lysine 9 at histone H3 in pericentromeric regions (53), and DNMT1 can bind to H3K9me3 and H3K27me3 at the promoter sites of ZEB2 [0.4 kb (3502) site] or Kruppel-like factor 4 (KLF4) [0.4 kb (3110) site] or Snail to inhibit EMT of prostate cancer (PCa) and hepatocellular carcinoma (HCC) (54,55). miR-185 and miR-148a can directly target DNMT1 so that the expression of breast cancer gene 1 (BRCA1) can be increased to stop the spread of breast cancer and gastric cancer (GC) (56).

In addition to the inhibitory effect of DNMT1, DNMT1 can also regulate the expression of some genes to promote tumor metastasis. For example, DNMT1 can bind to the nuclear transcriptional repressor CpG region of RAD9, which will promote the transcriptional expression of *RAD9* (a gene that maintains genome integrity, DNA repair, cell cycle checkpoints, apoptosis, and transcriptional transactivation of specific target genes) to promote metastasis of PCa cells (57). Osteopontin increases the expression of DNMT1 to increase the methylation of tumor-suppressor genes, Ras-associated domain family 1A (*RASSF1A*), GATA binding protein 4 (*GATA4*), cyclin-dependent kinase-like 2 (*CDKL2*), and death-associated protein kinase (*DAPK*) to induce metastasis of liver cancer and esophageal squamous cell carcinoma (ESCC) (58,59). Moreover, DNMT1 also reduces the expression of lncRNA-SPRY4-IT1 to promote gastric cancer cell migration and invasion (60). However, lncRNA-HNF1A-AS1 can bind to DNMT1 and inhibit its activation from promoting EMT of lung adenocarcinoma (61). SET and MYND domain-containing protein 2 (SMYD2) can increase adenomatous polyposis coli 2 (*APC2*) methylation by DNMT1 to activate the Wnt/ $\beta$ -catenin pathway, which promotes colorectal cancer (CRC) EMT (62).

*De novo* methylation and mammalian development require DNMT3a and DNMT3b (63). The target recognition domain (Trd) (residues R 831-f848), the catalytic loop (residues G 707-k721), and the homodimeric interface of DNMT3a mediate DNMT3a binding to DNA, and these loops come together to form a continuous DNA binding surface (64). Recognizing of CpG dinucleotides by DNMT3a is mediated by catalytic and TRD cycles (65). DNMT3b-mediated transcriptional repression occurs at CpG island (CGI)-associated promoters and repeats. The activity of DNMT3b is mainly to promote long-term gene silencing, which needs to be preserved in certain tissues to maintain the body's life (66). In addition to centromeric, pericentromeric, and subtelomeric repeats, germline genes are also known genomic targets of DNMT3b. Notably, the maintenance of CGI methylation of certain germ cell-specific genes in somatic cells depends entirely on DNMT3b activity (67). DNMT3a and DNMT3b also play an important role in tumor metastasis. For example, DNMT3a mutations are more common in acute myeloid leukemia (AML), and DNMT3A mutations can promote extramedullary infiltration (EMI) by upregulating the expression of TWIST1 (68). In addition, DNMT3a also regulates the expression of Snail and E-cadherin to affect the metastasis of GC (69). Metastasis-associated protein 1 (Mta 1) is one of the important chromatin remodeling factors in eukaryotic cells; it is one of the most upregulated oncogenes in human tumors and is involved in tumor progression and metastasis. Mta1 can inhibit the transcription of DNMT3a from increasing the expression

of insulin-like growth factor binding protein-3 (IGFBP-3), which promotes the metastasis of breast cancer (70). Smad4 and mastermind-like transcriptional coactivator 1 (MAML1) are novel direct targets of miR-34a and miR-133a-3p, but lncRNA-34a can bind to DNMT3a and inhibit the activity of miR-34a and miR-133a-3p, which increases Smad4 and MAML1 expression in HCC metastasis (71,72). In addition, DNMT3b also binds to the promoter region of miR-34, which enhances the expression levels of hepatocyte nuclear factor 4  $\gamma$  (HNF4G) and Notch1, which are downstream targets of miR-34a to promote migration and invasion of bladder cancer (73). Furthermore, lncRNA-H19 can directly bind to miR-29b-3p (miR-29b) and inhibit the expression of DNMT3b in bladder cancer cells. More importantly, upregulation of lncRNA-H19 was found to antagonize miR-29b-3p-mediated inhibition of breast cancer cell proliferation, migration and EMT. On the contrary, lncRNA-H19 knockdown partially reversed the effect of the miR-29b-3p inhibitor on Dnmt3b and promoted miR-29b-3p-induced MET (74). DNMT3b also can bind to the nuclear transcriptional repressor CpG region of RAD9 to promote metastasis of PCa cells (57).

Demethylation is one method of tumor prevention and treatment that involves restoring the activity of some key tumor suppressor or DNA repair genes. At present, DNMT inhibitors are the most studied, as they can reverse abnormal DNA methylation by inhibiting DNMT activity (75). The first phenotype-modifying drug, 5-azacytidine and its analog 5-aza-2'-deoxycytidine (5-aza-CdR), have been approved by the US FDA to treat preleukemic myelodysplastic syndromes (76). 5-Aza-CdR is an analog of cytosine, which can be incorporated into the DNA chain during DNA replication. On the one hand, it can reduce the ability of DNA to receive methyl groups, and on the other hand, it inhibits DNMT activity, resulting in the reduction in the DNA methylation level (77). It has been clinically shown that 5-aza-CdR can improve the survival rate of some patients with stage IV small cell lung cancer. However, the drug also has toxic and side effects that cannot be ignored (for example, the specificity is not strong, and it cannot be targeted for a specific tumor-suppressor gene; targeted therapy; high doses of 5-aza-CdR may induce tumor metastasis), so its clinical application is greatly limited (78). However, MCF-7 breast cancer cells were treated with the DNMT inhibitor 5-aza-cytidine to maintain a hypomethylated state. The results showed that the expression levels of pro-invasive EMT-associated genes related to the EMT process were upregulated, and the invasive and metastatic abilities of the cells were enhanced (79). The results of this study are worth serious deliberation. Although the use of DNMT inhibitors to treat tumors may inhibit the expression of proto-oncogenes, it may also increase the risk of tumor cell metastasis and dissemination. Therefore, we should use these drugs with caution in clinical practice.

#### *Metastasis regulated by histone modifications*

*Histone methylation and demethylation.* Histones protect genetic information, maintain DNA structure, and regulate gene expression. Histone amino-terminal (N-terminal) domains protrude from the nucleosome and can interact with other regulatory proteins and DNA. Histone modifications include methylation, phosphorylation, acetylation,

crotonylation, ubiquitination, glycosylation, and ADP ribosylation. Imbalances in histone modifications can lead to tumorigenesis, and loss of methylation, and acetylation of histone H3 and H4 residues has been shown to be a marker of tumor cells (80). Histone methylation and demethylation are usually carried out by histone methyltransferases (HMTs) and histone demethyltransferase (HDMs). The methylation of histones is a covalent modification of arginine and lysine. Arginines can be mono- or di-methylated, while lysines can be mono-, di-, or tri-methylated (81). There are three types of enzymes responsible for histone methylation, lysine-specific SET domain histone methylase, methylase of amino acid, and methylase of lysine (82). In general, the methylation of different sites of histone H3 and H4 and the amount of methylation have great significance for the transcriptional regulation of genes. Among them, H3K9me<sub>3</sub>, H3K27me<sub>3</sub>, and H4K20me<sub>2/3</sub> mediate transcriptional repression, while H3K4me<sub>1/2/3</sub>, H3K9me<sub>1</sub>, H3K27me<sub>1</sub>, H3K36me<sub>1/2/3</sub>, and H3k79me<sub>1/2/3</sub> mediate transcriptional activation (83).

According to the different amino acids catalyzed by histone transferases, HMTs can be divided into two families: protein lysine methyltransferases (PKMTs) and protein arginine methyltransferases (PRMTs). The KMT family is further divided into enzymes that contain SET domains, such as G9a, EZH2, DOT1L, SUV39H1, CLL8, MLL1, SET8, SETDB1, GLP, and SETD2; the PRMT family includes PRMT1-9 and CARM1 in mammals. HMTs have a direct regulatory effect on tumor development and metastasis (84). The enhancer of zeste homolog 2 (EZH2) gene can promote tumor development and is the catalytic component of the polycomb repressive complex 2 (PRC2). EZH2 utilizes its HMT activity to catalyze the trimethylation of histone H3 lysine 27, inhibiting the downstream tumor-suppressor genes such as E-cadherin, transforming growth factor- $\beta$  (TGF- $\beta$ ) receptor 2 (TGFBR2), P57, and PSP94 (85). However, EZH2 itself lacks enzymatic activity, and its activity requires the assistance of the zinc-finger-containing protein (SUZ12) and the WD40-repeat protein (EED) to maintain the integrity of the PRC2 complex and the methyltransferase activity of EZH2 (86). EZH2 binds phosphorylated p38 (p-p38) in breast cancer cells to other core members of PRC2, EED, and SUZ12. EZH2 overexpression leads to the expression of p-p38 and activates downstream pathway proteins, which promote breast cancer motility and metastasis (87). EZH2 overexpression inhibits the expression of metalloproteinase 2 (MMP-2) and promotes the proteolytic activity of MMP-2 and -9, which also promotes ovarian cancer invasion and migration (88). In addition, numerous studies have shown that EZH2 overexpression promotes the proliferation, migration, and invasion of cancer cells in lung, bladder, melanoma, and colorectal cancers (89,90). In addition to the high expression of EZH2, the low expression of some members of this family promotes tumor metastasis. For example, loss of SETD2 leads to persistent activation of AKT through extracellular matrix (ECM) production, thereby facilitating metastasis of pancreatic ductal adenocarcinoma (PDAC) (91). More importantly, loss of SETD2 can activate EZH2 signaling and AMPK signaling to promote PCa metastasis (92). KMT1E (also known as SETDB1) is involved in the epigenetic silencing of oncogenes and tumor-suppressor genes in cancer cells. KMT1E, a metastasis suppressor, is strongly downregulated

in highly metastatic lung cancer cells (93). In addition, SET8 (94), G9a (95), GLP (95), DOT1L (95), and MLL1 (96) have also been reported to be closely associated with tumor metastasis. The PRMT family also has members involved in tumor metastasis. PRMT1 can directly target the leukocyte adhesion molecule (ALCAM) to promote the growth and metastasis of melanoma (97). PRMT1, PRMT5, PRMT6, and PRMT7 can promote EMT of head and neck cancer, colorectal cancer, breast cancer, ovarian cancer, lung adenocarcinoma, and oral cancer cells (98-102).

HDMs also have a variety of domains, including Jumonji (N/C terminal domains) (83), PHD-finger, Zinc-finger, SWIRM1 (Swi3, Rsc, and Moira domains), and the amine oxidase domain (103). Lysine-specific demethylases (KDMs) work in concert with histone lysine methylases to maintain global histone methylation patterns. The histone demethylases characterized to date belong to the amine oxidase and oxygenase superfamilies. The amino oxidase family members degrade histones through flavin adenine dinucleotide (FAD)-dependent amine oxidase reaction substrate demethylation (104). The JmjC protein belongs to the family of oxygenases and demethylates histones in an  $\alpha$ -ketoglutarate and Fe(II) ion-dependent manner (105). Furthermore, they can also be divided into several families: UTY, KDM1A, KDM1B, KDM2A, KDM2B, KDM3A, KDM3B, JMJD1C, KDM4A, KDM4B, KDM4C, KDM4D, KDM5A, KDM5B, KDM5C, KDM5D, KDM6A, and KDM6B (45). Although not extensively studied as histone methylases, KDMs are also associated with tumor progression and metastasis. For example, KDM1A (also known as LSD1)-mediated stabilization of SEPT6 can activate the TGF- $\beta$ /SMAD pathway and VEGF-C/PI3K/AKT signaling pathway, to stability promote the metastasis of GC, non-small cell lung cancer (NSCLC), and breast cancer (106-108). At the same time, KDM2A and KDM2B can downregulate the expression of programmed cell death 4 (PDCD4) and active the TGF- $\beta$ /SMAD and PI3K/AKT/mTOR pathways to stabilize and promote the metastasis of GC, lung cancer, pancreatic cancer, and ovarian cancer (109-111). KDM3A and KDM3B can activate the Wnt/ $\beta$ -catenin pathway and upregulate c-MYC, lncRNA-MALAT1, and melanoma cell adhesion molecule (MCAM), and MCAM to promote CRC, Ewing sarcoma, and neuroblastoma migration and invasion (112,113). In addition to this, lysine-specific demethylases KDM4A (114) and KDM4B (115) are also closely related to tumor progression and metastasis.

In the past few years, specific inhibitors of a large number of different HMTs and HDMs have been developed. EZH2, DOT1L, PRMT1, PRMT5, LSD1, KDM2B, KDM4D inhibitors have entered the clinical trial stage. These results demonstrate that HMTs and HDMs play a critical function in tumor metastasis. Furthermore, we believe that more targeted drugs for HMTs and HDMs will enter the clinic in the future, bringing good news to patients.

*Histone acetylation and deacetylation.* Protein acetylation refers to the process of adding acetyl groups to protein lysine residues under the action of an acetyltransferase. Histone acetylation is a post-translational modification that mostly occurs at specific lysine residues in the basic amino acid concentration region at the N-terminal of core histones and transfers the

acetyl group of acetyl-CoA to  $sNH_3^+$  of lysine to neutralize a positive charge (116). Histone acetylation and deacetylation are usually carried out by histone acetyltransferases (HATs) and histone deacetylases (HDACs).

HATs can be divided into two families according to the properties of their substrates, the GNAT family (GCN5-related N-acetyltransferase family) and the MYST family (MOZ, Ybf2/Sas3, Sas2, and Tip60). Although both contain acetyl-CoA homologous sequences, there are differences in their core regions (117). Functionally, the GNAT family is mainly responsible for the acetylation of lysine sites on histone H3. In contrast, the MYST family is related to the acetylation of lysine sites (such as H4K16) on histone H4. According to the different domains contained, the MYST family can be divided into the following three types: the subgroup containing the plant homology domain (including MOZ and MORF), and the subgroup containing the chromatin domain (including Esa1, dMOF, and Tip60), and a subgroup containing zinc fingers (HBO1) (118). HATs facilitate the dissociation of DNA and histone octamers and the relaxation of nucleosome structure so that various transcription factors and co-transcription factors can specifically bind to DNA binding sites and activate gene transcription. Studies have shown that HATs are involved in tumor growth and metastasis. For example, lysine acetyltransferase 6A (KAT6A) can activate the Wnt/ $\beta$ -catenin pathway to promote the growth and metastasis of ovarian cancer (119). Histone acetyltransferase 1 (HAT1) and HBO1 can regulate the expression of TP53 to affect tumor metastasis (120).

HDACs deacetylate histones, bind tightly to negatively charged DNA, and make chromatin dense and coiled, repressing gene transcription (121). HDACs have been identified and grouped into four classes, including class I consisting of HDAC1, HDAC2, HDAC3, HDAC8; class II consisting of HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, HDAC10; class III consisting of SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, SIRT7; and class IV consisting of HDAC11 (122). Although HDACs can promote tumor metastasis, sometimes, some HDACs can also inhibit tumor metastasis. For example, HDAC1, HDAC2, HDAC4, HDAC5, and HDAC6 are required for both proliferation and metastasis of melanoma, pancreatic cancer, nasopharyngeal carcinoma, and hepatocellular carcinoma by downregulating E-cadherin (123-126). IRT7 is transcriptionally repressed by HDAC8, a novel cofactor of the SMAD3/4 complex, through local chromatin remodeling, further activating TGF- $\beta$  signaling and causing lung cancer metastasis (127). SIRT1 can promote the expression of ZEB1 to induce EMT of osteosarcoma (128). Overexpression of SIRT6 not only enhances the phosphorylation of extracellular signal-regulated kinase 1/2 (p-ERK 1/2) but also activates MMP 9 to promote tumor cell migration and invasion (129). SIRT6 also suppresses cell metastasis of pancreatic ductal adenocarcinoma (PDAC) by regulating the expression of HMGA 2, IGF2BP1, and IGF2BP3 (130). In addition, SIRT3 can activate FOXO3a and inhibit the wnt/ $\beta$ -catenin pathway, thereby inhibiting EMT of prostate cancer cells (131). SIRT4 inhibits Drp1 phosphorylation through interaction with fis-1, and suppresses MEK/ERK activity to inhibit NSCLC cell invasion and migration (132). SIRT7 is a key regulator of TGF- $\beta$  signaling and a suppressor of breast cancer metastasis, and its deletion promotes the metastasis of breast cancer cells (133).

Several HDAC inhibitors (HDACi) with different chemical structures have been purified from natural extracts or chemical synthesis. To date, there are at least nine different HDACi, including Saha, LAQ 824, FK 228, MS-275, CI-994, PXD 101, valproic acid, pyroxamine, and sodium butyrate, currently in use alone or in combination with therapy for blood disorders and solid tumors (134,135). HDACi selectively kills tumor cells and has little toxicity to normal cells. The basis for the selective toxicity of HDACi is unclear but may be related to the HDAC overexpression observed in cancer cells (2). HDACi has the ability to effectively activate multiple molecular pathways and mediate its antitumor effect (136,137). The antitumor effect of HDACi apparently depends on inhibiting the proliferation, survival, migration, invasion, metastasis, and angiogenesis of cancer cells by regulating gene transcription (138). In conclusion, the molecular basis for the tumor-selective cytotoxicity of HDACi has not been extensively studied; therefore, the molecular basis requires further in-depth validation.

#### *Metastasis regulated by ubiquitination and deubiquitination.*

Ubiquitination refers to the process in which the ubiquitin (a small 76-residue regulatory protein ubiquitously expressed in eukaryotes) molecule classifies proteins in cells under the action of a series of special enzymes, selects target protein molecules from them, and modifies explicitly the target protein (139). These special enzymes include ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), ubiquitin-protein ligase (E3), and degrading enzymes (140). Substrates can be modified with single ubiquitin (monoubiquitination) or polymeric Ub chains. Depending on which internal lysine (K6, K11, K27, K29, K33, K48, K63), or the N-terminal methionine residue of the Ub (m1, linear or head-to-tail) can be used to link to the far Ub chain type of end (141). Deubiquitinating enzymes (Dubs) balance ubiquitin chain growth by removing ubiquitin. The synergistic effect of Dubs recognition and Ub hydrolysis creates a dynamic network that controls the distribution of different ubiquitin signals, which in turn regulates numerous biological processes within the cancer cell (142). Approximately 103 Dubs have been recognized in the human genome, and they can be divided into six families according to their sequence and the sequence of conserved regions: USPs (ubiquitin-specific proteases) such as USP2, USP6, USP7, USP8, USP11, USP15, USP16, USP21, USP 28, USP35; UCHs (ubiquitin C-terminal hydrolysis enzymes) such as UCH-L1, UCH-L3, UCH-L5; MJDs (Machado-Josphin domain-containing proteases) such as JosD1, JosD1; OUTs (ovarian cancer proteases) such as A20, OTUB2, TRABIO; SENPs (motif-interacting with ubiquitin-containing novel DUB family), such as SENP1, SENP2, SENP8; JAMMs (JAB1, MPN, MOV34 family) such as AMSH (143).

Ubiquitination and deubiquitination play an essential role in protein localization, metabolism, function, regulation, and degradation. At the same time, it regulates nearly all life activities, including cell cycle, proliferation, apoptosis, differentiation, metastasis, gene expression, transcriptional regulation, signal transmission, damage repair, inflammation, and immunity (144). For example, E3 ubiquitin ligase RNF126 specifically regulates PTEN stability and then induces cell proliferation and metastasis of bladder cancer by upregulating the EGFR/PI3K/AKT signaling pathway (145). STAMBP

is a deubiquitinase (Dubs) family member in the Jab1/MPN family of metalloenzymes that specifically cleaves K63-linked polyubiquitinated chains from substrates to promote the stabilization of EGFR and the active AMPK signaling pathway to induce cell metastasis of lung adenocarcinoma (146). RING finger-domain E3 ubiquitin ligase RBBP6-mediated ubiquitination and degradation of I $\kappa$ B $\alpha$  enhances p65 nuclear translocation, triggering activation of the NF- $\kappa$ B pathway, which in turn induces EMT of colorectal cancer (147). In addition, some deubiquitinating enzymes can also play a role in promoting tumor metastasis. USP5 can induce EMT of non-small cell lung cancer (NSCLC) by activating the Wnt/ $\beta$ -catenin pathway (148). USP10 directly interacts with SMAD4 and stabilizes it to promote HCC proliferation and metastasis (149). USP21 can deubiquitinate and stabilize EZH2 to induce cell proliferation and metastasis of bladder cancer (150). USP11 promotes colorectal cancer growth and metastasis by stabilizing PPP1CA, activating the ERK/MAPK pathway, and insulin-like growth factor 2 mRNA binding protein 3 (IGF2BP3) signaling (151), and interacting with nuclear factor 90 (NF90) to promote HCC proliferation and metastasis (152). OTU domain-containing protein 3 (OTUD3), a deubiquitinating enzyme, also promotes HCC proliferation and metastasis by regulating  $\alpha$ -actinin 4 (ACTN4) (153). The deubiquitinating enzyme PSMD14 directly interacts with Snail and stabilizes it to promote cell migration and tumor metastasis of esophageal squamous cell carcinoma (154). In addition to their promoting effects, ubiquitinases and deubiquitinases can also inhibit tumor metastasis. For instance, E3 ligase zinc finger protein 91 (ZFP91) can regulate PKM splicing to inhibit HCC metastasis (155). Ubiquitin-conjugating enzyme variant proteins (Ube2v) and E3 ubiquitin ligase SMURF2 can degrade the protein level of SIRT1, thereby suppressing cell proliferation and metastasis of CRC (156,157). BTRC, an E3 ubiquitin ligase, can degrade the protein level of Twist1 to suppress cell proliferation and metastasis of GC (158).

The drug development of E3 ligase has been a very challenging research hotspot in recent years. At present, antitumor drugs targeting E3 ligase are mainly divided into four categories according to their mechanism of action: E3 ligase targeted inhibitors, E3 ligase targeted agonists, proteolytic targeting chimeras (PROTACs), and molecular glues (159). Considering the complex and extensive life activities regulated by ubiquitination, blocking or activating E3 ligase to treat tumors may have adverse effects on other everyday life metabolic activities. Therefore, exploring and solving this problem remains a considerable challenge. Moreover, most ubiquitination inhibitors found to be beneficial in preclinical studies have shown poor results in clinical trials. This discrepancy may be because we do not know enough about the target protein's structural analysis and medicinal chemistry, which requires technological advances.

Similarly, a large number of Dubs play an important role in the development of several stages of cancer development. The potential to affect processes such as signal transduction, proliferation, and apoptosis by affecting ubiquitination and proteasomal degradation of key regulators is promising and exciting. Dubs are more likely candidates than E3 ligases, which lack well-defined catalytic residues (160). For example, the first highly selective proteasome-bound USP14 inhibitor

uul(ubiquitin-7-amino-4-methylcoumarin, ub-amc) was identified by high-throughput screening of Ub-amc (161). P5091 (1-[5-[(2,3-dichlorophenyl)thio]-4-nitro-2-thienyl]-ethanone) was discovered to be a specific inhibitor of USP7 for the first time. This compound inhibits the stabilizing effect of USP7 on Hdm2 and exerts a pro-apoptotic effect by stabilizing p21 and p53 (162). Betulinic acid (BA) [(3 $\beta$ )-3-hydroxy-lup-20(29)-en-28-oc acid] is a naturally occurring plant-derived compound with proapoptotic and highly specific effects on cancer cells. BA was identified as a broad inhibitor of deubiquitination that induces apoptosis by releasing mitochondrial proteins and leads to the downregulation of angiogenic markers (163). Overall, USPs are a complex system, and not all components have been adequately evaluated. It is well known that the UPSs are involved in almost all tumor cell processes. There are many important clinical implications to new ways to target UPS in cancer therapy, and we expect that UPS-based therapy will play a significant role on a clinical level in the near future.

*Metastasis regulated by glycosylation.* Abnormal glycosylation plays a vital role in the key pathological processes of tumorigenesis and development (Fig. 3) (164). Glycans play important roles in tumor cell signaling, tumor cell separation and invasion, cell-matrix interaction, angiogenesis, metastasis, and immune regulation, and abnormal glycosylation is often referred to as a 'signature of cancer' (165). The synthesis of N-linked sugar chains starts in the endoplasmic reticulum and is completed in the Golgi apparatus. Most of the mannose in the original sugar chain is excised, but various glycosyltransferases add different types of sugar molecules, in turn, to form oligosaccharide chains with different structures (166). The spatial structure of a glycoprotein determines which glycosyltransferase it can bind to undergo specific glycosylation modifications (167). Many glycoproteins have both N-linked sugar chains and O-linked sugar chains (168). The O-linked glycosylation is carried out in the Golgi apparatus; usually, the first linked sugar unit is N-acetylgalactose, and the linked sites are the hydroxyl groups of Ser, Thr, and Hyp, and then the sugar groups are successively transferred to it to form an oligosaccharide chain; the donor of sugar is also a nucleoside sugar, such as UDP-galactose (169). As a result of glycosylation, different proteins are marked differently, changing the polypeptide's conformation and increasing the protein's stability (170). Metastatic tumor cells must undergo a series of important events, including EMT, detachment from the primary tumor mass, adherence to ECM proteins, migration and degradation of ECM proteins, invasion of adjacent tissues, penetration of lymphatic or blood vessels, spread to different parts of the body, and outflow from blood vessels to form metastatic tumors (171). In humans, there are more than 2,000 proteins that contain an amino acid motif suitable for N-glycosylation. They are either membrane-bound or secreted but by no means cytoplasmic or nuclear. Therefore, glycoproteins are critical for tumor metastasis (172). Examples of N-glycans are secreted proteinases such as kallikreins, carboxypeptidase E, cathepsins, and others; adhesion proteins including members of the immunoglobulin superfamily (ALCAM, ICAM1, BCAM, and others), cadherins; Wnt family members; c-Kit, TIMP1, tetraspanins, clusterin, and others; ECM



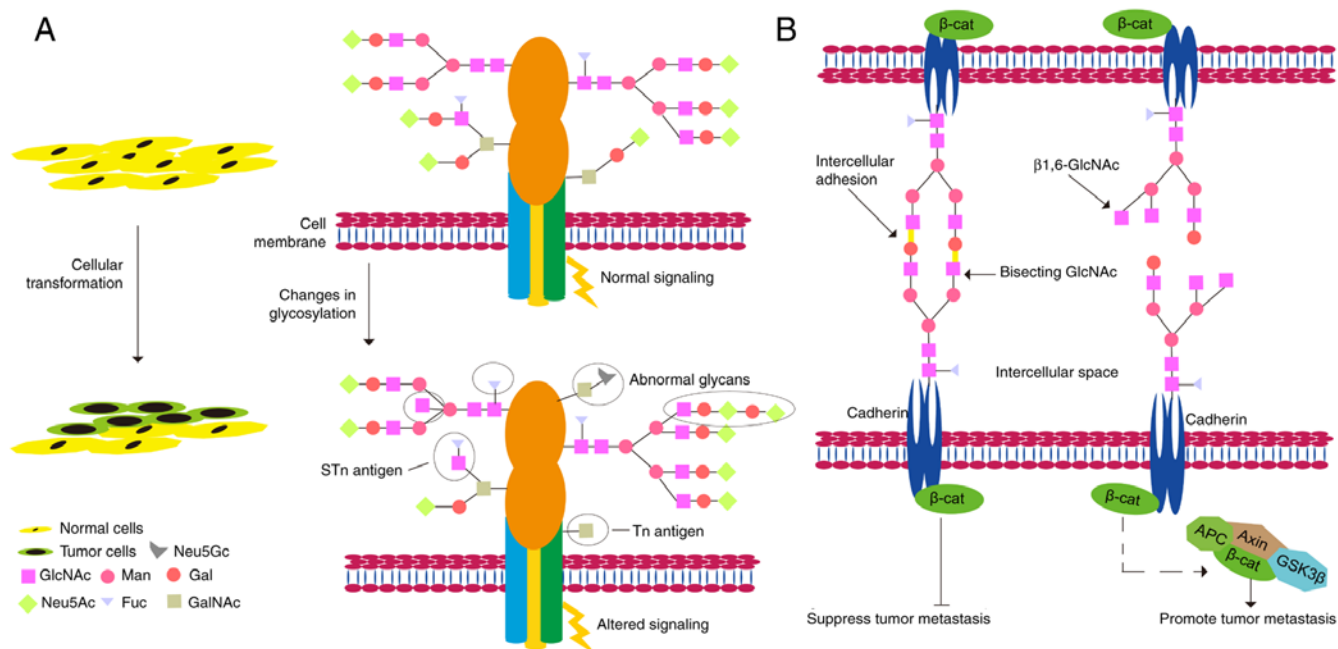


Figure 3. Glycosylation and tumor metastasis. (A) The effect of glycosylation on the transformation of normal cells into tumor cells. (B) Effects of glycosylation on the transformation of tumor cells into metastatic tumor cells.  $\beta$ -cat,  $\beta$ -catenin; APC, adenomatous polyposis coli; GSK3 $\beta$ , glycogen synthase kinase 3 $\beta$ .

molecules such as fibronectin, laminin, and others (173). N-glycosylated cadherins have substantial effects on their functions as adhesion molecules, signaling proteins, and tumor suppressors (174). Human E-cadherin displays four potential N-glycosylation sites (175). Moreover, alterations in the expression profiles of E-cadherin-linked N-glycans are associated with malignant and invasive phenotypes and poor survival in cancer patients (176). Another important part of N-glycosylation is that it helps keep N-cadherin stable. It also plays a role in preventing cell-cell adhesion and promoting GBM cell migration (177).

The ECM is the acellular part of tissue composed of collagen, glycoproteins, proteoglycans, and crevices. Dynamic changes in cell-ECM interactions, including those coordinated by glycans, are critical for tumor cells to acquire migratory and invasive capabilities (178). The integrin family encompasses the primary surface receptors involved in the adhesion of cells to the ECM elements. N-linked glycans modulate integrin function regulating the migration capacity of tumor cells (179). ST6GAL1 (ST6  $\beta$ -galactoside  $\alpha$ -2,6-sialyltransferase 1), which catalyzes the transfer of sialic acids to terminal galactose residues of N-glycans, is upregulated, which can increase the migration and invasion of human CRC cells (180).

Similarly, ST6GAL1 can increase adhesion to ECM structures and increase the invasiveness of breast cancer (181). N-glycosylation of N-acetylglucosaminyltransferase V enhances CD 147/basigin interaction with integrin  $\beta$ 1 to promote liver cancer metastasis (182). Cluster of differentiation 147 (CD147) is an extracellular matrix metalloproteinase inducer, and modification of N-glycosylation of Asn152 on CD147 strongly promotes invasion and migration of HCC (183). Of course, in addition to the promoting effect, N-glycosylation also has an inhibitory effect on the metastasis of tumor cells. For example, glycosylation of Asn-144 of Golgi protein 73 (GP73) inhibits HCC metastasis (184).

O-glycosylation has the same effect on tumor cell metastasis as N-glycosylation. For instance, GalNAc-type O-glycosylation can modify TGF- $\beta$  to facilitate breast cancer cell migration and invasion via the EMT process (184). N-acetylgalactosaminyltransferase 6 (GALNT6), an enzyme that mediates the initial step of mucin-type O-glycosylation, enhances O-glycosylation of  $\alpha$ 2-macroglobulin ( $\alpha$ 2M) and activates the downstream PI3K/Akt signaling pathway to promote migration and invasion of breast cancer and ovarian cancer (185,186). However, N-acetyl-galactosaminotransferase 2 (GALNT2), an enzyme that initiates O-glycosylation of mucins, inhibits metastasis of gastric adenocarcinoma by reducing EGFR-AKT signaling (187). Osteopontin (OPN) is a multiphosphorylated extracellular glycoprotein. O-terminal glycosylation of OPN can increase cell adhesion, thereby inhibiting tumor cell metastasis (188).

As glycosylation is implicated in every link from tumor occurrence to metastasis, antitumor medication development for glycosylation, such as cancer-related glycoforms and glycosyltransferases related to synthetic sugars, which are all potential therapeutic targets is urgently needed (189). Glyco-lectin interactions are central axes of multiple aspects of cancer progression, such as immune evasion, cell proliferation, invasion, and extravasation. Blocking this interaction is a promising new strategy for single-agent and combination therapy (190). Finally, we emphasize that in addition to the need to develop new cancer drug strategies targeting glycosylation, it is worth exploring efficient cancer delivery systems to avoid side effects. We believe that exploring specific glycosylation targets may be the beginning of a new era in cancer therapy.

*Metastasis regulated by phosphorylation and dephosphorylation.* Phosphorylation and dephosphorylation are some of the most prevalent chemical modifications in cells and are catalyzed by phosphorylase and phosphatase, respectively (191).

Protein phosphorylation is a ubiquitous regulatory mechanism in organisms. It plays an important role in various aspects of every organism, such as gene transcription, expression, cell proliferation, differentiation, apoptosis, signal transduction, immune regulation, tumor occurrence, and transfer (192). Phosphorylation refers to the addition of a phosphate ( $\text{PO}_4$ ) group to a protein or other types of molecules, which can also be defined as 'introducing a phosphate group into an organic molecule' (193). Protein phosphorylation can be divided into four categories according to the amino acid residues that are phosphorylated: phosphorylation of serine, threonine, and tyrosine constitutes O-phosphorylation; phosphorylation of histidine, arginine, and lysine constitutes N-phosphorylation; phosphorylation of aspartate and glutamate constitutes S-phosphorylation; phosphorylation of cysteine constitutes acyl phosphorylation (192). More than 90% of the proteins encoded by the human genome are phosphorylated. Therefore, phosphorylated or dephosphorylated proteins can regulate tumor growth and metastasis.

For example, phosphorylation of cyclase-associated protein 1 (CAP1) can induce EMT of lung cancer (194). Longevity assurance homolog 2 of yeast LAG1 (LASS2), a novel tumor-suppressor gene, is thought to be a ceramide synthase that synthesizes very long acyl-chain ceramides. Therefore, phosphorylated LASS2 inhibits Wnt/ $\beta$ -catenin signaling to reduce prostate cancer growth and metastasis (195). Protein phosphatase 2A (PP2A)-induced dephosphorylation of girdin is involved in inhibiting breast cancer cell migration (196).

Signaling pathways regulated by protein kinases are involved in the occurrence and development of almost all types of cancer. Therefore, the study of kinase-mediated signaling pathways and the possibility of blocking them with targeted therapy may have important clinical therapeutic implications, especially since many of these proteins are oncogenes (197). The signaling networks through which protein kinases operate are very complex, but we believe that understanding the regulatory functions of kinases may be an effective means of identifying more effective cancer treatments (198). Many drug kinase inhibitors, such as imatinib mesylate (199), crizotinib (200), vemurafenib, and cobimetinib (201), are already on the market; nevertheless, their efficacy is often reduced due to the development of complex resistance mechanisms (202). In short, protein phosphatase may be a new drug target for treating malignant tumors in the future.

*Metastasis regulated by chromatin remodeling.* Chromatin remodeling refers to the molecular mechanism of changes in the packaging state of chromatin, histones in nucleosomes, and corresponding DNA molecules during the replication and recombination of gene expression (203). Chromatin remodeling can lead to changes in the position and structure of nucleosomes, causing chromatin changes. ATP-dependent chromatin remodelers reposition nucleosomes, alter nucleosome structure, and covalently modify histones (204). In the process of nucleosome remodeling, the role of the remodeling factor complex (ATPase activity) is crucial, including the SWI/SNF family, ISWI family, CHD family, and INO80 family (205). These shared properties enable nucleosome engagement, selection, and remodeling. Each ATPase family catalyzes a different remodeling activity which can include incremental

nucleosome sliding on DNA in *cis*-ribosomes; DNA loops generated on the surface of nucleosomes; histone H2A/H2B dimers cleared; histone VIII aggregates are cleared, or histone octapeptide subunits are exchanged within the nucleosome to alter their composition (206). Each of these activities alters the accessibility of DNA in chromatin to DNA-binding factors, which in turn regulate fundamental nuclear processes such as transcription, DNA replication, and DNA repair.

The chromatin remodeling activity of ATPases usually occurs in a large multi-subunit complex, but they are called single ATPase subunits in rare cases. Complexes in the SWI/SNF family include the large multi-subunit BAF, PBAF, and WINAC complexes, which are co-regulators of transcription and which also contribute to DNA damage repair (207). Like SWI/SNF, members of the INO 80 family are large multi-subunit complexes that regulate transcription, but their roles in DNA damage repair are more pronounced (208). These complexes are unique among ATP-dependent remodeling complexes in that they catalyze the exchange of histones from the nucleosomal structure. Complexes with optimal function include SRCAP and Tip 60/P 400, which exchange H2A/H2B histone dimers found in standard nucleosomes for variant H2A.Z/H2B dimers (209,210). The CHD family contains nine different ATPases and is the largest in the remodeling family. The most characteristic complex in this family is NURD (211). NURD contains both ATP-dependent chromatin remodeling and HDAC activities (211). MBD2 is a unique subunit of the NURD complexes and can bind 5mC DNA (212). Once recruited by 5mC-enriched DNA, the MBD2-NURD complex inhibits gene expression through its remodeling and histone deacetylase activity. MBD3 can replace the MBD2 subunit, dissociating NURD from 5mC and promoting its function as a transcriptional activator (213). Most imitation switch (ISWI) complexes are relatively small, consisting of only two or three subunits. Each of these complexes contains a large subunit with several histone-binding domains (including PHD and bromodomains) and an ISWI family of ATPases (214). These complexes have multiple functions, including spacing of nucleosomes after DNA replication (CHRAC, ACF), RNA polymerase elongation (RSF), as co-regulators of transcription (CERF, NURF, NoRC, b-WICH) and regulation of DNA damage repair (WICH) (215).

All proteins involved in chromatin remodeling also share five basic properties: a) domains that recognize covalent histone modifications; b) an affinity for the nucleosome, beyond DNA itself; c) domains and/or proteins that regulate the ATPase domain; d) a similar DNA-dependent ATPase domain, required for remodeling and serving as a DNA-translocating motor to break histone-DNA contacts; and e) domains and/or proteins for interaction with other chromatin or transcription factors (205).

The role of chromatin remodeling in cancer metastasis is well-studied (216). For example, chromatin remodeling protein BRG1, a core component of the mammalian chromatin remodeling complex, regulates the transcription of long-chain fatty acid elongase 3 (Elovl3), which promotes cell metastasis of PCa (217). MORC family CW-type zinc finger 2 (MORC2) is a newly discovered chromatin remodeling protein that promotes breast cancer invasion and metastasis through interacting with catenin delta 1 (CTNND1, also known as p120-catenin, was

originally identified as a substrate of the oncogenic tyrosine kinase Src and subsequently defined as a component of the adherens junction complex that includes E-cadherin and  $\alpha$ -,  $\beta$ -,  $\gamma$ -catenins) (218). However, chromatin remodeling factor ARID2 is one subunit of the chromatin-remodeling SWI/SNF complex and inhibits EMT of HCC cells by recruiting DNMT1 to Snail promoter, which increases promoter methylation and inhibits Snail transcription [55]. ARID1A, a SWI/SNF chromatin remodeling complex subunit, inhibits cancer cell migration, invasion, and metastasis by downregulating  $\beta$ -catenin signaling (219).

Signaling pathways regulated by chromatin remodeling proteins are involved in the occurrence and development of almost all types of cancer. Changes in chromatin structure have profound effects on gene expression during normal cellular homeostasis and malignant transformation. Therefore, screening small molecules targeting recombinant chromatin proteins has important clinical implications.

*Metastasis regulated by non-coding RNAs.* Non-coding RNAs (ncRNAs) refer to RNAs that do not encode proteins. These include RNAs with known functions such as rRNA, tRNA, circular RNA, snRNA, snoRNA, and microRNA and RNAs with unknown functions (220). The common feature of these RNAs is that they can all be transcribed from the genome but not translated into proteins to perform their respective biological functions at the RNA level. Non-coding RNAs can be divided into three categories in terms of length: less than 50 nt, including microRNAs, siRNAs, piRNAs; 50-500 nt, including rRNAs, tRNAs, snRNAs, snoRNAs, siRNAs, srpRNAs; greater than 500 nt, including long non-coding RNAs, long non-coding RNAs without polyA tails (221).

MicroRNA is a class of 21-23 nt small RNAs, its precursor is approximately 70-100 nt, forming a standard stem structure, and after processing, it becomes a 21-23 nt single-stranded RNA. The mechanism of action of a microRNA is to complement mRNA, silencing or degrading mRNA (222). snRNA is short for small nuclear RNA. Its function is to combine with protein factors to form small nuclear ribonucleoprotein particles (snRNPs) and perform the function of splicing mRNA. There are mainly five types of snRNAs: U1, U2, U4, U5, and U6 (223). snoRNAs are the first small RNAs discovered in the nucleolus, called small nucleolar RNAs, and their biological functions were initially discovered to modify rRNA. Most small nucleolar RNAs can be divided into two categories. One is C Dbox snoRNA, which is methylated on RNA bases. It contains 4 Boxes: Box C, Box D, BoxC' and BoxD'. The other type is the H/ACA box. This type of snoRNA carries out methyluracilylation modification to the base of RNA. Its characteristic is to form a double stem and add a loop area in the middle, among which boxH in the middle loop area (224). Long non-coding RNAs (lncRNAs) are longer than 200 bp and are transcribed from independent promoters by RNA Pol II (225). Its sequence conservation is not high, and its expression abundance is low, showing strong specificity in tissues and cells. lncRNAs are involved in various critical regulatory processes such as X chromosome silencing, genomic imprinting, chromatin modification, transcriptional activation, transcriptional interference, and intranuclear transport (226). Unlike known linear RNAs, circular RNAs (circRNAs) form

a covalently closed continuous loop. In circRNAs, the 3' and 5' ends of the RNA molecule are usually joined together. This property confers several properties on circRNAs, many of which have only recently been identified. Many circRNAs are derived from protein-coding genes, but some studies have shown that some circRNAs can encode proteins (227). Because circRNAs were previously found to have no protein-coding function, they were classified as non-coding RNAs. Recently, some circRNAs have shown potential as gene regulators (228).

There are many studies showing that non-coding RNAs can regulate tumor growth and metastasis. Over the past decade, the regulatory roles of lncRNAs and miRNAs in various biological processes have emerged. The regulatory mechanisms of lncRNAs and miRNAs are diverse, relying primarily on their localization and interacting proteins or RNAs (229,230). For many metastasis-related miRNAs, target genes with established roles in tumor cell invasion, migration, and metastasis have been identified, such as MMPs, HER receptors, BMPs, PTEN, ZEB1, ZEB2, or E-cadherin (231). Some metastasis-related genes are directly or indirectly regulated by multiple miRNAs simultaneously. For example, members of the miR-200 family (miR-141, miR-200a, miR-200b, miR-200c, miR-429) have been shown to regulate the epithelial properties of cells by silencing Zeb proteins (232), and ZEB1/ZEB2 are also affected by regulation of miR-205 and or miR-192 (233).

lncRNAs are abnormally regulated in many cancers and are associated with tumor metastasis. lncRNAs can be used as new biomarkers for tumor diagnosis and treatment. Using lncRNA arrays or RNA-seq analysis, many lncRNAs have been found to be markers of tumor prognosis (234). More and more studies have shown that lncRNAs are potent regulators of EMT during tumor metastasis by controlling key molecules in several intracellular signaling pathways, including TGF- $\beta$ /SMAD, Wnt/ $\beta$ -catenin, Notch, MEK/ERK, PI3K/AKT, and JAK/STAT, notably Snail, ZEB and TWIST, which inhibit the expression of epithelial state-associated genes while simultaneously activating the expression of mesenchymal state-associated genes and concomitantly (235-238).

Since miRNAs play critical roles in tumorigenesis and metastasis, they are likely to be tumor-suppressor targets or therapeutic drugs. In the case of abnormal upregulation, miRNAs can be silenced by directly targeting miRNAs involved in tumor pathogenesis by 'anti-miRNA' molecules. Conversely, when miRNAs aberrantly downregulate mRNAs that directly target genes involved in tumor pathogenesis, so-called miRNA mimics or similar drugs can be used as drugs to replace pathologically downregulated miRNAs (231). Furthermore, to date, research on lncRNAs and metastasis has mainly focused on different organ-specific metastases. However, the reality is that many patients suffer from or are at risk for multi-organ metastases. In addition, the function of lncRNAs can be altered through epigenetic modification and microenvironmental shift (239). This complexity makes it difficult to fully understand the specific molecular mechanisms of tumor metastasis mediated by lncRNAs (240). Because lncRNAs are mediators of tumor metastasis, targeting them as a common therapeutic target in different types of tumors may be important for future research.

#### 4. Conclusion

Epigenetic regulation and metastasis play unique roles in the occurrence and development of tumors, and related enzymes and regulatory factors are potential drug targets for cancer treatment. Although no single epigenetic regulator is mutated in tumor metastasis, there is growing evidence that metastatic tissue has a distinct epigenetic status compared to the primary tumor tissue for use in cancer therapy and diagnosis (241). Due to the nature of epigenetic modifications, modulating these changes and understanding the role of epigenetics in EMT and metastasis will provide new insights into our understanding of tumor progression and metastasis. Because epigenetic modifications are reversible, a thorough understanding of their function in EMT provides us with new insights into tumor progression and metastasis. In addition, it can further facilitate the development of human cancer diagnostic and therapeutic strategies. Epigenetic alterations associated with EMT are considered clinically as a potential biomarker. Given the complexity of epigenetic transformation, we also need to pay special attention to the epigenetic characteristics of the target protein or RNA when using targeted drugs, which means that our drugs need to be more cautious. Nevertheless, we believe that a detailed understanding of the epigenetic aspects of EMT regulation and metastasis will undoubtedly be an excellent way to develop prognostic cancer biomarkers. Moreover, the development of specific inhibitors of enzymatic proteins designed by epigenetic modification will also be new hope for treating tumor metastasis.

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#### Availability of data and materials

All information provided in this review is documented by relevant references. All references are open-ended articles.

#### Authors' contributions

HC and YC contributed to the conception and design of the review. TT and PS organized the database and wrote the first draft of the manuscript. MNA, YW and JX wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

#### Ethics approval and consent to participate

Not applicable.

#### Patient consent for publication

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#### Competing interests

The authors declare that there are no competing interests.

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