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Role of DNA Methyltransferases (DNMTs) in metastasis

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ABSTRACT

The DNA methyltransferase (DNMT) family constitutes a conserved set of DNA-modifying enzymes which have essential functions in the modulation of epigenetics. The fundamental role of epigenetic changes in carcinogenesis and metastasis is increasingly being appreciated. DNMTs (DNMT1, DNMT3A and DNMT3B) have been shown to drive metastasis. Epigenetic machinery is installed at the target sites for the regulation of a wide variety of genes. Moreover, microRNAs, long non-coding RNAs and circular RNAs also shape the epigenetic landscape during metastasis. In this review, we have provided a snapshot of the quintessential role of DNMTs in metastasis. We also summarize how lncRNAs and circRNAs play roles in the epigenetic regulation of a myriad of genes.

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Introduction

Tracking the landscape of gene control in single cells and individual patients have disentangled complex information and exciting insights about somatic and inherited mutations in cancer and extrachromosomal oncogene amplification (1). Moreover, drug resistance and loss of apoptosis are also central drivers of carcinogenesis and metastasis (2-7). Pioneering studies have shown that drug resistance, loss of apoptosis and cancer metastasis co-operate and reinforce each other in the invasion niche and persist upon metastatic evasion.

Increasingly it is being realized that cancer cells have a highly deregulated DNA-methylation landscape.

DNMTs catalyze the transfer of methyl groups to cytosine nucleotides within CpG sequences in the strands of DNA, resulting in alteration in conformations. These conformational changes inhibit the binding of transcriptional factors thus causing the repression of the expression levels of methylated gene networks. Characteristically, DNMTs include DNMT1, which keeps pre-existing methylation status. Whereas, DNMT3A and DNMT3B led to the establishment of de novo methylation. The comprehensive mechanistic insights of epigenetic regulatory mechanisms in the context of cancers have been extensively reviewed elsewhere (8-15).

In this mini-review, we take a broad overview of the epigenetics field, highlighting current topics of interest ranging from the fundamental role of DNMTs in metastasis and how different non-coding RNAs play a central role in epigenetic modifications.

DNMT1

Total DNMT1 levels remained unchanged in bone metastatic RCC cells (**16**). However, there was an evident increase in the accumulation of DNMT1 in mitochondria. Collectively, these results clearly indicated that hypermethylation of the mtDNA in bone metastatic tumor cells is because of the accumulation of DNMT1 in mitochondria. 5-Aza

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pre-treated bone metastatic RCC cells did not induce skeleton metastases when injected through the left cardiac ventricle (16).

Ecotropic viral integration site-1 (EVI1) is a zinc-finger transcription factor (17). EVI1 has been shown to transcriptionally downregulate TIMP2 (tissue inhibitor of matrix metalloproteinase-2) (Fig.1). DNMT1 worked synchronously with EVI1 and epigenetically inactivated TIMP2. Mice injected with 5-aza-2'-deoxycytidine-treated COLO 205 cells showed fewer metastatic nodules in the liver, skin and small lesions behind the lungs. Importantly, the volume of metastatic skin nodules was considerably smaller in size in 5-aza-2'-deoxycytidine-treated groups (17).

RACGAP1 (Rac GTPase Activating Protein 1) has a highly conserved RhoGAP domain. Essentially, the RhoGAP domain switches on GTPase activities of Rho family kinases/proteins (RHOA/RAC1/CDC42) and converts GTP-bound proteins into GDP-bound forms (18). ERK1/2 phosphorylation was found to be enhanced greatly in RACGAP1-overexpressing MCF7 cancer cells. RACGAP1 overexpression in MCF7 cells caused an increase in phosphorylation of DRP1-S616 but total DRP1 levels remained unchanged. PLK1 (Polo-like kinase-1) phosphorylates a wide variety of substrates. Phosphorylation of RACGAP1 by PLK1 creates docking sites for ECT2. RACGAP1-ECT2 interactions are essential for the activation of the downstream ERK1/2-DRP1 transduction cascade. PGC-1a is involved in the mitochondrial translocation of DNMT1, which consequently enhances mitochondrial DNA (mtDNA) methylation. There was an evident increase in mtDNMT1 in RacGAP1-expressing-MCF7 cells, whereas mtDNMT1 levels were reduced in RacGAP1-silenced- MCF7 cancer cells. Tail vein injections of RacGAP1-expressing-MCF7 cells and RacGAP1-expressing-MDA-MB-231 cells led to a notable increase in the lung colonization of cancer cells (18).

EZH2-recruited DNMT1 mediated hypermethylation of DNA led to epigenetic inactivation of tumor suppressor miR-484 (Fig.1) (19). Overexpression of EZH2 evoked an increase in the levels of H3K27me3 and occupancies of EZH2 in the miR-484 upstream region, whereas EZH2 knockdown led to marked suppression of H3K27 trimethylation and binding of EZH2 to the upstream regions of miR-484. MMP14 (matrix metalloproteinase) and HNF1A (hepatocyte nuclear factor 1A) are directly targeted by miR-484 (19).

LINC00922 potently inhibited NKD2 by attachment of DNMT1, DNMT3A/DNMT3B at the NKD2 promoter (Fig.1) (20). There was an evident increase in the pulmonary and liver metastases in mice inoculated with LINC00922-overexpressing or NKD2-silenced MCF-7 cancer cells. Importantly, very few cancer cells showed a tendency to metastasize to the liver in siRNA-LINC00922-treated experimental models (20). Findings clearly indicated that overexpression of LINC00922 or NKD2 knockdown facilitated the metastasizing potential of cancer cells in mice whereas, LINC00922 silencing led to suppression of the metastatic properties of cancer cells in mice.

ARID2 (AT-Rich Interaction Domain 2) efficiently inhibited migration and invasion of HCC cells (21). ARID2 recruited DNMT1 to SNAIL promoter and epigenetically inactivated its expression. 6-thioguanine and 5-azacitidine mediated inhibition of DNMT1 caused an increase in levels of SNAIL in ARID2-overexpressing MHCC97-H and PVTT cancer cells. Importantly, intrahepatic metastasis mouse models are useful in the analysis of the role of oncogenes and tumor suppressors in HCC metastasis. Lung seeding was evidently reduced in mice injected with ARID2-expressing MHCC97-H cancer cells. Whereas, there was a notable increase in metastatic seeding in mice injected with ARID2-silenced-PLC/PRF/5 cancer cells. Hepatic deletion of ARID2 significantly increased pulmonary metastases in N-nitrosodiethylamine-induced HCC rodent model (21).

DNA demethylation led to the recruitment of CTCF (CCCTC-binding factor) to MEG3-DMR (maternally expressed gene 3 differentially methylated region), which acted as a cis-regulatory element for 14q32 miRNA expression (22). Importantly, miRNA-655-3p and miRNA-554a are constitutively overexpressed in COLO320-DM cancer cells. Intrasplenically injected COLO320-DM cells did not cause liver metastasis in experimental mice. Ectopic expression of 14q32 miRNAs miRNA-127-5p, miRNA-369-3p, miRNA-544a or

miRNA-655-3p in HCT116-L2T cells caused a reduction in liver metastasis (22).

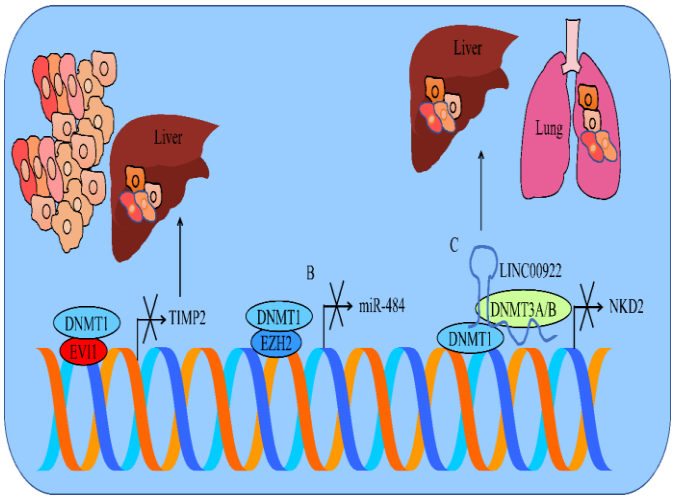

Figure 1. (A) DNMT1 worked synchronously with EVI1 and epigenetically inactivated TIMP2. Inhibition of TIMP2 promoted metastasis. (B) EZH2-recruited DNMT1 and epigenetically inactivated tumor suppressor miR-484. (C) LINC00922 potently inhibited NKD2 by attachment of DNMT1, DNMT3A/DNMT3B at the NKD2 promoter. Inhibition of NKD2 promoted liver and pulmonary metastasis.

DNMT3A

In a recent study, MeDIP-seq and hMeDIP-seq analyses were conducted for the detection of the genes modulated by dynamic DNA methylation (23). Promoter hypomethylation led to upregulation of CD147 and promoted cancer progression. KLF6 works in an orchestrated manner with MeCP2 and DNMT3A to form a multi-protein complex for the repression of CD147 expression in normal tissues. Demethylation of DNA is catalyzed by TDG (thymine DNA glycosylase) and Tet (ten-eleven translocation). TGFβ induced active demethylation led to the removal of KLF6/MeCP2/DNMT3A. Moreover, TGFβ promoted the binding of SP1, ten-eleven translocation-1, TDG as well as SMAD2/3 transcriptional machinery to the promoter region of CD147 (Fig.2). CRISPR RNA-guided Cas9 nuclease target sites use small base-pairing guide RNAs and cause cleavage of DNA fragments in a sequence-specific manner. Interestingly, the research team designed dCas9-SunTag-DNMAT3A-sgCD147 specific methylation systems for the recruitment of DNMT3A to promoter regions and subsequent remodeling of DNA methylation. The injection of NSCLC cells into the airways of the mice led to the development of orthotopic lung cancer models. NCI-H460 cells severely triggered osteolytic bone lesions as well as significant bone destructions within femur bones of control mice. Whereas, targeted methylation of CD147 revealed a marked reduction in tumor lesions and bone damage. Targeted methylation (epigenetic inactivation) of CD147 in cancer cells led to considerable suppression of metastases signals in the limbs. Moreover, mice with targeted methylation of CD147 demonstrated a notable reduction in bone metastases and reduced osteolytic areas as compared to the control group of rodent models (23).

Sohlh2 is a family member of basic-loop-helix bHLH protein transcription factors (24). Overexpression of Sohlh2 downregulated the expression of DNMT3a and consequently upregulated Klotho in renal cell carcinoma cells (Fig.2). Overexpression of Sohlh2 inhibited RCC tumor growth in xenografted mice. Sohlh2 overexpression markedly reduced the number of hepatic and pulmonary metastatic lesions (24).

miR-133a-3p directly targeted MAML1 (25). MAML1 upregulated DNMT3A levels. Furthermore, MAML1 increased epigenetic inactivation of miRNA-133a-3p through DNMT3A in MDA-MB-231 and MCF-7 cancer cells (Fig.2). Metastasis was assessed by bioluminescent imaging in animal models injected with MAML1-overexpressing-cancer cells. Fluorescent intensity levels of the liver and lungs were considerably weaker in mice injected with miRNA-133a-3p-overexpressing cancer cells as compared to the mice injected with MAML1-overexpressing-cancer cells. Metastatic lesions derived from MAML1-overexpressing- MDA-MB-231 cancer cells were bigger in size. Essentially, these larger lesions were noticed in the livers and lungs, whereas smaller masses were found to be disseminated in livers and lungs of mice injected with miR-133a-3p overexpressing cancer cells (25).
MYC promoted the binding of DNMT3A to the miRNA-200b promoter, resulting in proximal CpG island hypermethylation and consequent epigenetic inactivation of miR-200b (26). DNMT3A knockdown led to an increase in miR-200b expression via promoter demethylation. Enforced expression of miR-200b markedly inhibited the

migratory and invasive properties of MDA-MB-231 cancer cells (26).

LINC00470 promoted the binding of MYC and DNMT3A to the promoter region of PTEN and epigenetically inactivated it (27). Importantly, lung metastatic nodules were significantly reduced in mice injected with LINC00470-silenced endometrial cancer cells (27).

IRX1, a tumor suppressor has been reported to be frequently downregulated in gastric cancer (28). PRMT5 (protein arginine methyltransferase 5) worked synchronously with DNMT3A and epigenetically inactivated IRX1. Abdominal nodular amounts were markedly reduced in mice injected with PRMT5-silenced-NCI-N87 cancer cells. Mice injected with PRMT5-silenced-NCI-N87 cancer cells showed fewer peritoneal nodules. Likewise, there was a significant reduction in pulmonary metastasis in experimental mice injected with PRMT5-silenced-NCI-N87 cancer cells (28).

DNA methyltransferase 3A isoform b (DNMT3Ab) plays a central role in metastasis (29). DNMT3Ab mediated epigenetic repression of E-cadherin via DNA hypermethylation. There was a marked increase in the levels of H3K9me2 and H3K27me3. Whereas, DNMT3Ab depletion efficiently restored E-cadherin expression and reversed TGFβ-induced EMT by a reduction in the levels of DNA methylation, H3K9me2 and H3K27me3 at the promoter region of E-cadherin. Metastasis experiments provided evidence of reduced metastatic spread in mice injected with DNMT3Ab knockdown cancer cells (29).

DNMT3B

MAEL (maelstrom), an oncogene has been shown to promote metastasis (30). MAEL overexpression enhanced metastatic spread of urothelial carcinoma of the bladder (UCB). MAEL overexpression in UCB cells substantially enhanced the enrichment of HDAC1, HDAC2 and DNMT3B on the promoter of MTSS1 and epigenetically inactivated MTSS1. Additionally, miRNA-186 is a negative regulator of MAEL and miR-186 downregulation is an alternative underlying cause for MAEL overexpression in UCBs. There was a marked increase in the metastatic tumor nodules on the surface of the lungs in mice injected with MAEL overexpressing-5637- cancer cells (30).

There was a reduction in H3K9ac levels and a simultaneous increase in H3K27me3 occupancy at MAML2 (31). Stilbenoids prevented the binding of OCT1 to the enhancer region of MAML2. DNMT3B loading at MAML2 enhancer was found to be enhanced by stilbenoids (31).

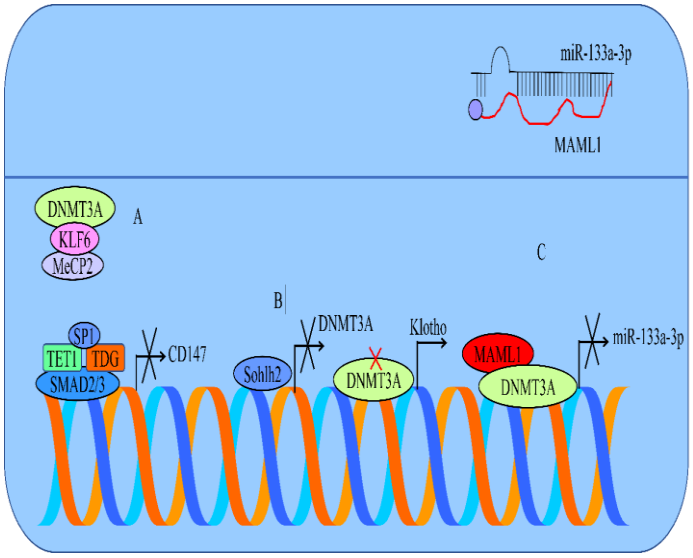

Figure 2. (A) TGFβ induced active demethylation led to the removal of KLF6/MeCP2/DNMT3A. Moreover, TGFβ promoted the binding of SP1, TET1, TDG as well as SMAD2/3 transcriptional machinery to the promoter region of CD147. Promoter hypomethylation led to upregulation of CD147 and promoted cancer progression. (B) Sohlh2 downregulated DNMT3A and promoted the expression of Klotho. (C) MAML1 increased epigenetic inactivation of miRNA-133a-3p through DNMT3A

Forkhead box C1 (FOXC1) upregulated the expression of DNMT3B to induce DNA hypermethylation of promoter of CTH (cystathionine γ-lyase) (32). FOXC1 is transcriptionally upregulated by ELK1. ERK1/2 inhibitors effectively reduced the binding of ELK1 to the promoter region of FOXC1. DNMT3B silencing eliminated HCC metastases with Huh7-FOXC1 cells which prolonged the overall survival rate of tumor-bearing mice. Contrarily, DNMT3B overexpression rescued the inhibition of HCC metastases in mice injected with FOXC1-silenced-MHCC97H cancer cells (32).

SLC34A2 interacted directly with Cortactin and these interactions significantly increased the recruitment of ARP2/3 and N-WASP, consequently providing the trigger for the invadopodia formation

and degradation of the matrix (33). Overexpression of SLC34A2 caused an increase in p-PI3K, p-AKT and phosphorylation of FOXO3a at Serine-253 and blocked its nuclear accumulation. SLC34A2 overexpression led to the exit of FOXO3a from the nucleus to the cytoplasm in TPC-1 cells but this process was abolished by AKT inhibitors. In contrast to an increase in the number of pulmonary metastatic nodules in mice injected with SLC34A2-overexpressing cancer cells, suppression of Cortactin considerably blocked lung metastasis and improved overall survival rates of experimental mice. Tail-vein injections of SLC34A2-knockdown BCPAP cancer cells clearly suggested that SLC34A2 inhibition potently reduced pulmonary metastasis lesions (33).
DNMT3B epigenetically repressed tumor suppressor miR-432-5p (34). There was a marked reduction in metastasis in lung tissues and liver tissues in mice injected with DNMT3B-silenced LoVo or HCT116 cancer cells (34).

DNMT3B also transcriptionally downregulated miR-451a in bladder cancer cells (35). miR-451a has been shown to target and negatively regulate EPHA2. EPHA2 activates PI3K/AKT cascade, thus driving carcinogenesis and metastasis of bladder cancer cells (35).

Regulation of DNMTs by non-coding RNAs

Noncoding RNAs do not encode proteins but produce noncoding transcripts that modulate gene expression and protein functions. microRNAs (miRNAs) (36-45), long non-coding RNAs (LncRNAs) (46-50) and circular RNAs (51-55) have gained appreciation because of their central role in carcinogenesis and metastasis.

Interestingly, the past few years have witnessed quantum leaps forward in our knowledge about underlying molecular mechanisms of microRNA-induced gene silencing and how lncRNAs and circular RNAs interfere with miRNA-mediated targeting of DNMTs. Here, we review the recent advancements in the identification of interplay between lncRNAs/circular RNAs and miRNA targets and the emerging paradigms of how lncRNAs and circular RNAs shape the dynamics of epigenetics.

Long non-coding RNAs

The detection of RNA-chromatin association in a genome-wide manner combined with chromatin conformation capture technologies have unraveled complicated long non-coding RNA-mediated control of chromatin architecture and epigenetic modifications of target genes.

LncRNA PVT1 interacted with DNMT1 and epigenetically inactivated BNIP3 (56). LncRNA PVT1 knockdown inhibited the proliferation potential of gastric cancer cells. Methionine deficiency led to significant downregulation of lncRNA PVT1. Methionine deficient diet-induced suppression of the tumor mass in mice inoculated with MKN45 cells. Levels of lncRNA PVT1 in the tumor tissues were noted to be significantly downregulated in the mice fed with methionine-free diets (56).

Following the activation of the Hippo pathway, MST1/2 is phosphorylated and sequentially activates LATS1/2 (57). LATS1/2-mediated phosphorylation of YAP/TAZ prevented nuclear accumulation of YAP/TAZ. DLG3 activated the Hippo signaling pathway. DLG3 interacted with MST2 and regulated LATS1-mediated inhibition of nuclear accumulation of YAP. MIAT, an oncogenic lncRNA worked synchronously with DNMT1, DNMT3A and DNMT3B and repressed the expression of DLG3. MIAT knockdown considerably reduced the weights and volumes of tumor xenografts in experimental mice, while MIAT overexpression led to an increase in tumor development in xenografted mice (57).

GIHCG worked synchronously with EZH2 and DNMT1 and epigenetically inactivated miR-200b/a/429 by increasing the trimethylation of H3K27 and DNA methylation levels (58). Different clones of SMMC7721 cancer cells were intra-splenically injected into nude mice for analysis of liver metastasis. GIHCG overexpression caused an increase in the liver metastases burden, which was abolished by ectopic expression of miR-200b/a/429. Moreover, different clones of SMMC7721 cancer cells were directly injected into the tail veins of experimental mice. Findings indicated that GIHCG overexpression induced an increase in pulmonary metastasis burden, but an ectopic expression of miR200b/a/429 led to marked suppression of pulmonary metastasis (58).

SP1 transcriptionally upregulated SPRY4-IT1 (59). Importantly, SPRY4-IT1 antagonized miR-101-3p-mediated targeting of EZH2. EZH2 along with LSD1 (lysine-specific demethylase 1) or DNMT1 were recruited by SPRY4-IT1 and regulated the expression of LATS2 and KLF2. SPRY4-IT1 directed the attachment of EZH2 and DNMT1 to the KLF2 promoter region and inactivated it. Moreover, SPRY4-IT1 also triggered the accumulation of LSD1 and EZH2 to LATS2 promoter regions and inhibited its transcription. Tumorigenesis was notably suppressed in mice xenografted with SPRY4-IT1-silenced-HuCCT1 cancer cells (59).

Design and development of pharmacologically efficient molecules which can bind lncRNAs with higher specificity and affinity depends on the characterization of specific RNA motifs with structural complexities. Importantly, sophisticated information is thus far only available for fewer lncRNAs, suggesting that lncRNAs have the ability to undergo folding into different modular domains for various molecular interactions. Moreover, synthetic molecules that mimic the binding and structural features of lncRNAs act as decoys. These decoys compete with lncRNAs for binding with epigenetic-modifying machinery and thus blocking its functions.

Circular RNAs

DNMT1

circ_0040809 blocked miR-515-5p-mediated inhibition of DNMT1. circ_0040809 silencing inhibited proliferation and migration of colorectal cancer cells (60).

Circ-DNMT1 interfered with miR-485-3p-induced targeting of ZEB1. There was an evident reduction in the tumor growth in mice inoculated with circ-DNMT1-silenced-MDA-MB-231 cancer cells (61).

DNMT3A

circ0093740 enhanced carcinogenesis and metastasis by blockade of miR-136/145-mediated targeting of DNMT3A in Wilms tumor (62). circ0093740 suppression inhibited the metastatic capacity of G401 and SKNEP1 Wilms tumor cells in lung metastasis experiments (62).

Likewise, circ_0084615 antagonized miR-599-mediated inhibition of DNMT3A in colorectal cancer cells (63). Tail vein injections of circ_0084615-silenced HCT116 cancer cells led to a marked reduction in pulmonary metastasis (63).

circIQCH sequestered miR-145 and promoted breast cancer progression by upregulation of DNMT3A (64). Inhibition of circIQCH led to notable suppression in the number of pulmonary metastatic nodules (64).

Concluding remarks

Overcoming acquired or inherent resistance to standard therapies is principally imperative given that patients have a disease-free or progression-free survival. Multi-pronged approach/multi-targeted therapy has shown promise in improving the clinical outcome of these agents significantly, as evaluated in phase I and phase II of clinical trials exploring DNMT inhibitors or HDAC in combination with chemotherapeutic drugs or small-molecule inhibitors.

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None

Conflict interest

The authors declare no conflict of interest.

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