

Epigenetic and epitranscriptomic role of lncRNA in carcinogenesis (Review)

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Abstract. Long non-coding RNAs (lncRNAs) are key players in the regulation of gene expression by mediating epigenetic and epitranscriptomic modification. Dysregulation of lncRNAs is implicated in tumor initiation, progression and metastasis. lncRNAs modulate chromatin structure and gene transcription by recruiting epigenetic regulators, including DNA- or histone-modifying enzymes. Additionally, lncRNAs mediate chromatin remodeling and enhancer-promoter long-range chromatin interactions to control oncogene expression by recruiting chromatin organization-associated proteins, thereby promoting carcinogenesis. Furthermore, lncRNAs aberrantly induce oncogene expression by mediating epitranscriptomic modifications, including RNA methylation and RNA editing. The present study aimed to summarize the regulatory mechanisms of lncRNAs in cancer to unravel the complex interplay between lncRNAs and epigenetic/epitranscriptomic regulators in carcinogenesis. The present review aimed to provide a novel perspective on the epigenetic and epitranscriptomic roles of lncRNAs in carcinogenesis to facilitate identification of potential biomarkers and therapeutic targets for cancer diagnosis and treatment.

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1. Introduction

Long non-coding RNAs (lncRNAs) are transcribed by RNA polymerase II and range in length from 200 nucleotides to 100 kilobases without coding for proteins (1); ~95% of the human genome consists of nc sequences that are transcribed into lncRNAs (2). These lncRNAs can be classified into long intergenic nc (linc), enhancer, intronic and antisense lncRNAs (3). Additionally, lncRNAs modulate gene expression involved in multiple biological processes, including cell apoptosis, proliferation and differentiation and post-transcriptional, translational and epigenetic regulation (4,5).

lncRNAs play important roles in regulating chromatin structure and oncogene expression, thereby contributing to tumorigenesis (6). Mechanistically, lncRNAs directly recruit epigenetic and/or epitranscriptomic regulators to control oncogene expression, driving tumor development and progression (7). Rapid advancements in genome-wide technologies are accelerating identification of novel lncRNAs and their regulatory mechanisms in carcinogenesis. Notably, lncRNAs are involved in epigenetic regulation by modifying chromatin structures (primarily acetylation and methylation) through specific enzymes, including DNA- and histone-modifying enzymes, and chromatin organization-associated proteins (8). Furthermore, lncRNAs are essential for modulating the three-dimensional (3D) genomic architecture (9). CCCTC binding factor (CTCF), regulated by lncRNAs, serves as a master regulator of mammalian chromatin topologically associated domain (TAD) (10). CTCF controls oncogene expression by mediating chromatin TAD architecture and enhancer-promoter contacts within TADs (11). CTCF contains RNA-binding regions (RBRs) within its zinc finger (ZF) domains recognized by lncRNAs, which are key for CTCF self-clustering and CTCF-mediated long-range chromatin interaction (12,13). Deletion of RBRs notably disrupts half of CTCF mediated chromatin loops to cause deregulation

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of gene expression (12). lncRNAs cooperate with CTCF to mediate genome topological regulation, thereby leading to carcinogenesis (9). lncRNAs also regulate oncogene expression and carcinogenesis by recruitment of epitranscriptomic regulators, including RNA-modifying enzymes mediating RNA N6-methyladenosine (m⁶A) modification and RNA adenosine-to-inosine (A-to-I) editing (14). Thus, future studies may elucidate the interlocking functions of lncRNAs with both epigenome and epitranscriptome to develop novel cancer therapies and improve prognostic strategies (15).

Understanding the epigenetic and epitranscriptomic regulatory roles of lncRNAs in carcinogenesis is key for unraveling the molecular mechanisms underlying cancer development and progression. The present review aims to provide a comprehensive overview of how lncRNAs influence gene expression in carcinogenesis and their potential as diagnostic markers and therapeutic targets in oncology.

2. lncRNA recruits epigenetic regulators contributing to carcinogenesis

lncRNAs play key roles in mediating DNA modification, histone modification and chromatin organization to regulate oncogene expression in cancers. lncRNAs recruit DNA- and histone-modifying enzymes and chromatin organization-associated proteins at specific genomic loci to modulate gene expression in carcinogenesis (5,7,16-18).

lncRNAs interact with DNA-modifying enzymes in carcinogenesis. DNA methylation is a critical epigenetic process in which methyl groups are added to cytosine residues to form 5-methylcytosine (5mC) modification in the DNA sequence, particularly in promoter CpG islands (19). This modification serves a key role in epigenetic regulation, specifically in controlling oncogene expression and influencing tumor development and progression (20). In cancer, there are five types of DNA methyltransferases (DNMTs) involved in DNA 5mC modification, namely DNMT1, DNMT2, DNMT3A, DNMT3B and DNMT3L (21). Abnormal DNA methylation patterns, such as hypermethylation of tumor suppressor genes or hypomethylation of oncogenes, are associated with the onset and progression of various types of cancer (19). For example, hypermethylation reduces the expression of *p16(INK4a)* in melanoma (22), the *BRCA1* gene is hypermethylated in breast cancer (23), and the *Myc* gene is hypomethylated in hepatocellular carcinoma (HCC) (24).

DNMT3s, specifically DNMT3A and DNMT3B, serve a crucial role in initiating DNA methylation (25). These lncRNAs reprogram the DNA 5mC methylation landscape, facilitate DNA self-assembly, and serve as universal cancer biomarkers to promote carcinogenesis (20). Mechanistically, lncRNAs recruit DNMT3A and DNMT3B to target oncogenes and influence methylation status of their promoters and regulatory regions (16) (Fig. 1A). lncRNA *ADAMTS9-AS2* recruits DNMT3s to the cadherin 3 promoter CpG islands, thereby decreasing proliferation, invasion and migration of esophageal cancer cells (26). lncRNA *HOTAIR* regulates *MTHFR* (methylene tetrahydrofolate reductase) gene expression by recruiting DNMT3s to mediate DNA methylation at the *MTHFR* gene promoter, conferring chemoresistance in

esophageal cancer (27) (Fig. 1B). Additionally, *lnc34a* recruits DNMT3A and prohibitin 2 to silence microRNA (*miR*)-34a expression, promoting colorectal cancer proliferation (28). lncRNA *TTTTY15* mediates DNMT3A to increase 5mC modification at *TBX4* promoter, leading to dysregulation of *TBX4* gene expression associated with non-small cell lung cancer (NSCLC) cell proliferation and metastasis (29). lncRNA *ASIDHRS4* enhances DNA methylation at the *DHRS4L2* (Dehydrogenase/reductase member 4 like 2) promoter region to suppress the *DHRS4* gene expression in carcinogenesis (30). lncRNA *MROS-1* modulates *PRUNE2* (prune homolog 2 with BCH domain) expression to enhance oral cancer migration by interacting with DNMT3A (31). lncRNA *IRAIN* inhibits *VEGFA* expression to suppress renal carcinoma tumor growth by recruitment of DNMT3A/B to the *VEGFA* promoter region (32). Collectively, lncRNAs serve a critical role in recruiting DNMT3s to mediate aberrant DNA methylation patterns in cancer development and carcinogenesis (Fig. 1B).

Notably, lncRNAs serve a critical role in maintaining DNA 5mC methylation in cancer genome by recruiting DNMT1 (Fig. 1C) (25). For example, lncRNA *HAGLR* functions as a tumor suppressor by recruiting DNMT1 to the promoter of E2F Transcription Factor 1) gene, inhibiting lung adenocarcinoma cell proliferation (33) (Fig. 1C). Depletion of lncRNA *LUCAT1* promotes the ubiquitination of DNMT1 and enhances expression of *UHRF1* (Ubiquitin Like with PHD and Ring Finger Domains 1) gene in esophageal squamous cell carcinoma (34). Additionally, loss of *CCDC26* (Coiled-Coil Domain Containing 26) results in genome-wide hypomethylation, increasing double-stranded DNA breaks and inducing hepatocellular carcinoma cell death (35). Similarly, lncRNA *DBCCR1-003* inhibits DNA methylation at the *DBCCR1* (Deleted in bladder cancer chromosome region 1) promoter region by sequestering DNMT1, decreasing bladder cancer cell proliferation (36). lncRNA *H19* mediates DNA methylation and *NAT1* (N-acetyltransferase 1) gene expression, contributing to breast cancer chemoresistance (37). Moreover, lncRNA *PVT1* recruits DNMT1 to the miR-18b-5p DNA promoter, forming the *PVT1* (plasmacytoma variant translocation gene 1)/miR-18b-5p/*HIF1A* (hypoxia inducible factor 1 subunit alpha) regulation axis in gallbladder cancer (38), suggesting its potential therapeutic role (38). Thus, lncRNAs play critical roles in cooperation with DNMT1 methyltransferase to maintain DNA 5mC methylation and regulate oncogene expression in the cancer genome (Fig. 1C).

Additionally, ten-eleven translocation (TET) family proteins (TET1, TET2 and TET3) oxidize 5mC to 5-hydroxymethylcytosine, activating DNA demethylation (39,40) (Fig. 1D). Previous studies have highlighted a subset of lncRNAs that interact with TETs to regulate DNA demethylation in carcinogenesis (41-43). For instance, lncRNA *Oplrl6* recruits TET2 to the *OCT4* (Octamer-Binding Transcription Factor 4) promoter, mediating promoter-enhancer loops regulation of *OCT4* expression in tumorigenesis (44). Similarly, lncRNA *Platr10* interacts with TET1 to mediate DNA demethylation at the *OCT4* promoter (45). Additionally, lncRNA *TETILA* mediates TET2 subcellular localization by binding to the double-stranded β -helix domain in acute myeloid leukemia (AML) (42). lncRNA *MAG12-AS3* recruits TET2 to the *LRIG1* (leucine rich repeats and immunoglobulin

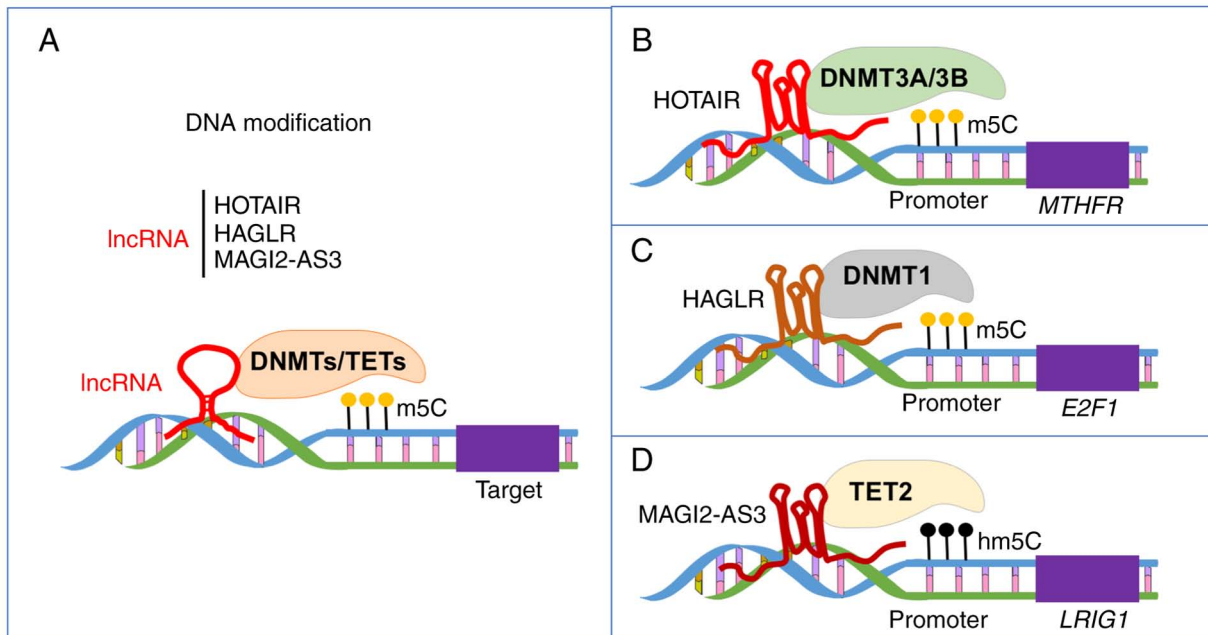


Figure 1. lncRNAs recruit DNA modifying regulators to modulate the expression of target genes in cancer genome. (A) In cancer, lncRNAs directly recruit DNMTs/TETs to induce DNA methylation or demethylation, respectively. (B) lncRNA *HOTAIR* directly recruits DNMT3A/3B modifying complex to regulate *MTHFR* and *GSTP1* gene expression in esophageal cancer. (C) lncRNA *HAGLR* directly interacts with DNMT1 to modulate the expression of *E2F1* gene in lung adenocarcinoma cells, thereby decreasing cell proliferation. (D) lncRNA *MAGI2-AS3* recruits TET2 to activate *LRIG1* gene expression, thereby decreasing leukemic stem cell proliferation. Inc (long non-coding); DNMT (DNA Methyltransferase); TET (Ten-eleven translocation); m5C (5-methylcytidine); MTHFR (methylenetetrahydrofolate reductase); GSTP1 (glutathione S-transferase P1); hm5C (5-hydroxymethylcytidine).

like domains 1) promoter, upregulating *LRIG1* expression and inhibiting leukemic stem cell (LSC) proliferation (46) (Fig. 1D). lncRNA *RUNXOR* triggers DNA demethylation and activates expression of *RUNX1* gene to suppress breast cancer proliferation by interacting with TETs (47). In short, lncRNAs are key for regulating the DNA demethylation in tumorigenesis by recruiting TET family proteins (Fig. 1D).

Collectively, lncRNAs exert their influence by interacting with DNA-modifying enzymes. Dysregulation of DNA-modifying enzymes alters the epigenetic landscape of the genome, driving cancer development and progression. Specifically, lncRNAs promote DNA methylation or demethylation at promoters of the tumor suppressor or activator genes by interacting with the DNMTs or TETs, thereby inducing carcinogenesis (Fig. 1A-D; Table SI).

lncRNA interacts with histone-modifying complex in carcinogenesis. lncRNAs interact with histone-modifying complexes, which catalyze reversible histone modification, regulating chromatin accessibility, DNA replication and gene transcription during the development and progression of cancer (48). The histone modifications are catalyzed by histone-modifying complexes, including ‘writer’ and ‘eraser’ proteins. Writer proteins comprise histone methyltransferases (HMTs) and histone acetyltransferases (HATs), which deposit methyl and acetyl groups on the lysine-rich amino-terminal tails of histone proteins, respectively. By contrast, eraser proteins include histone demethylases and deacetylases, which can remove the aforementioned groups. lncRNAs directly interact with histone-modifying enzymes to modulate gene expression associated with cell proliferation, cell cycle progression, apoptosis and metastasis (Fig. 2A).

lncRNA *HOTTIP* serves a vital role in the activation of posterior *HOXA* (Homeobox A) genes by facilitating the recruitment of the WD Repeat Domain 5)/MLL (Mixed-Lineage Leukemia)/DOT1L (DOT1 Like Histone Lysine Methyltransferase) complex in AML leukemogenesis (18,49) (Fig. 2B). lncRNA *HOXBLINEC* recruits the MLL/SETD1A (SET Domain Containing 1A) complex to induce the expression of *HOXB4* oncogene in AML (50) (Fig. 2C). Furthermore, the oncogenic lncRNA *RUNXOR* enriches histone H3K4me3 (Trimethylation of Histone H3 at Lysine 4) at the *RUNX1* promoter, driving the progression of breast cancer (47). Additionally, lncRNA *LINC02273* mediates H3K4me3 modification to enhance the transcription of the anterior gradient protein 2 homolog) oncogene, promoting breast cancer metastasis (51,52). lncRNA *ROR* directly recruits the histone methyltransferase MLL1 to upregulate *TIMP3* (Tissue Inhibitor of Metalloproteinases 3) expression, contributing to breast cancer proliferation and progression (53). lncRNA *MIAT* (Myocardial Infarction Associated Transcript) recruits MLL to the promoter region of the collagen degradation enzyme *MMP9* to reduce proliferative capacity and cell migration in NSCLC (54). lncRNA *LAMP5-AS1* binds DOT1L to increase H3K79me2/me3 levels, promoting MLL cell proliferation (55). In short, lncRNAs serve key roles in activation of cancer-associated genes by recruiting histone methyltransferase complexes, including MLL and DOT1L (Table SI).

lncRNAs are key players in regulating gene expression and impacting various cellular processes. Specifically, lncRNAs serve critical roles in silencing oncogene expression by recruiting H3K9me or H3K27me-associated histone methyltransferase complexes. For example, lncRNA *PHACTR2-AS1*

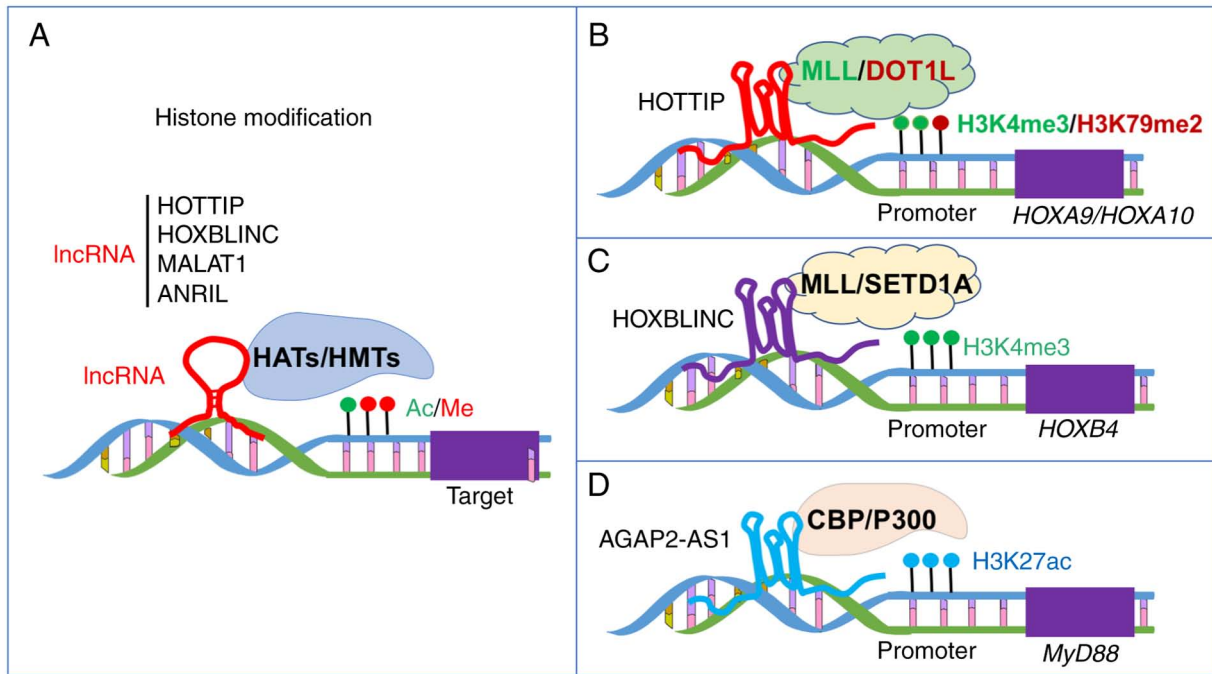


Figure 2. lncRNAs recruit histone modifying regulators to mediate gene expression in cancer genome. (A) lncRNAs directly recruit HMTs or HATs to mediate histone modification in cancer. (B) lncRNA *HOTTIP* recruits MLL/DOT1L complex to regulate *HOXA9* and *HOXA10* oncogene expression in AML leukemogenesis. (C) lncRNA *HOXBLINEC* recruits the MLL/SETD1A complex to regulate *HOXB4* oncogene expression in AML. (D) lncRNA *AGAP2-AS1* recruits the CBP/P300 complex to regulate *MyD88* oncogene expression, driving breast cancer progression and chemoresistance. lnc (long non-coding); HMT (Histone methyltransferase); HAT (Histone acetyltransferase); MLL (mixed lineage leukemia)/Dot1L (DOT1 Like Histone Lysine Methyltransferase); HOX (Homeobox); AML (acute myeloid leukemia); SETD1A (SET domain containing protein 1A); CBP (CREB-binding protein); Ac/Me (Acetylation or methylation); H3K4me3 (Trimethylation of Histone H3 at Lysine 4).

mediates H3K9me of ribosomal DNA, leading to the suppression of rRNA transcription and inhibiting cell proliferation and metastasis of breast cancer by recruiting EZH2 (Enhancer of Zeste Homolog 2) (56,57). Similarly, the antisense ncRNA *Kcnq1ot1* interacts with polycomb repressive complex (PRC2) components EZH2, SUZ12 (suppressor of zeste 12 homolog), and G9a to silence the potassium voltage-gated channel subfamily Q member 1 gene, contributing to tumorigenesis (58). Furthermore, lncRNA *HOTAIR* lncRNA has been implicated in promoting tumor progression and metastasis in various types of cancer, including breast and pancreatic cancer, NSCLC and gastrointestinal stromal tumor (59-62). Mechanistically, *HOTAIR* recruits PRC2 and LSD1 (Lysine specific demethylase 1)/REST corepressor 1) epigenetic complexes to increase H3K27me3 and decrease H3K4me2 to downregulate *p21* expression (63-66). Moreover, lncRNA *FEZF1-AS1* specifically binds LSD1 to regulate the expression of *CDKN1A* gene, contributing to pathogenesis of colorectal carcinoma, glioma and gastric cancer (67). lncRNA *Air* recruits G9a enzyme to mediate H3K9 methylation at the *Slc22a3* (Solute carrier family 22 member 3) gene promoter, thereby repressing *Slc22a3* expression in carcinogenesis (51). lncRNA *EPB41L4A-AS2* regulates *RARRES1* (Retinoic acid receptor responder 1) and *MyD88* via H3K27me3 modification to suppress breast cancer invasion and metastasis (68). lncRNA *MALAT1* suppresses *E-cadherin* expression to promote osteosarcoma (OS) metastasis by interacting with PRC2 complex component EZH2, embryonic ectoderm development gene) and SUZ12 (69,70). lncRNA *ANRIL* interacts with PRC1 and PRC2 complexes to suppress gene transcription, including

p15/CDKN2B, *p16/CDKN2B* and *p14ARF* gene clusters (71,72). lncRNA *PANDA* interacts with PRC1, PRC2 and the transcription factor NF-YA (Nuclear transcription factor Y, alpha) to suppress senescence in cancer cells (73). *HOTAIR* interacts with PRC2 complex to silence its target gene expression by increasing H3K27me3 enrichment in its target loci in breast cancer cells (62,74). Critically, lncRNA could also regulate histone modification via histone acetyltransferase in cancer cells. lncRNA transcribed upstream of the *CCND1* gene recruits translocated in liposarcoma to the *CCND1* promoter region and suppresses *CCND1* transcription by inhibiting the histone acetyltransferase CBP (CREB Binding Protein)/p300 in tumorigenesis (75). lncRNA *circAGFG1* recruits EZH2 to inhibit *p53* gene expression, regulating proliferation and cell cycle progression in cervical cancer (76). lncRNA *LINC01419* interacts with EZH2 to mediate the histone methylation at the reversion-inducing cysteine-rich protein with kazal motifs) promoter, controlling hepatocellular carcinoma growth and metastasis (77). lncRNA *lnc-ATB* directly binds EZH2 to regulate cell proliferation, invasion and migration in ovarian cancer (78). lncRNA *LINP1* recruits EZH2 to the promoter regions of tumor suppressors *KLF2* (KLF transcription factor 2) and *PRSS8* (Serine protease 8), regulating cell apoptosis in cervical cancer (79). lncRNA *XIST* facilitates cell proliferation, migration and invasion in neuroblastoma by interacting with PRC2 complex to downregulate *DKK1* (Dickkopf-1) gene expression (80). lncRNA *UCA1* confers tamoxifen resistance in breast cancer through regulation of the EZH2/p21 axis and the PI3K/AKT signaling pathway (81). lncRNA *AGAP2-AS1* mediates the H3K27 acetylation at the

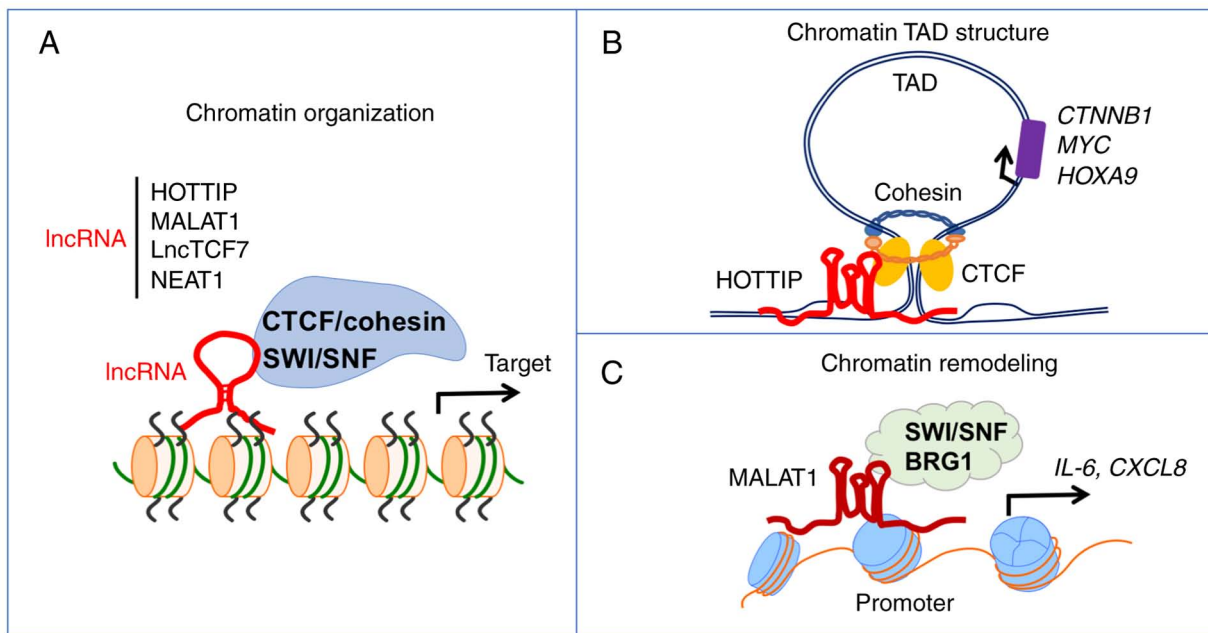


Figure 3. lncRNAs interact with chromatin organization-associated regulators to mediate gene expression in cancer. (A) lncRNAs directly recruit CTCF/cohesin or SWI/SNF complex to mediate chromatin organization and gene expression in cancer. (B) lncRNA *HOTTIP* interacts with CTCF/cohesin complex to regulate *HOXA9* and WNT target expression in acute myeloid leukemia leukemogenesis. (C) lncRNA *MALAT1* interacts with chromatin remodeling protein BRG1 to regulate *IL-6* and *CXCL8* expression, promoting hepatocellular carcinoma progression. Inc (long non-coding); CTCF (CCCTC-binding factor); SWI/SNF (SWItch/Sucrose Non-Fermentable); HOX (Homeobox); BRG1 (Brahma-related gene 1); CXCL8 (C-X-C Motif Chemokine Ligand 8); TAD (topologically associating domain); CTNNB1 (Catenin Beta 1).

promoter of the carcinogenic protein MyD88 by binding with CBP, resulting in progression and chemoresistance of breast cancer (82) (Fig. 2D; Table SI).

Collectively, lncRNAs not only serve important roles in contributing to carcinogenesis by recruiting the H3K4me3 or H3K79me2-related HMT complexes, MLL and DOT1L, but also interact with chromatin PRC2 or PRC1 complex leading to suppressed gene expression in carcinogenesis (Fig. 2A-D; Table SI). The interaction between lncRNAs and histone-modifying enzymes represents a novel and complex regulatory network in carcinogenesis. Further research into the mechanisms underlying these interactions may provide valuable insights into the molecular mechanisms driving cancer development and potentially lead to the identification of the novel drug targets for cancer therapeutics.

lncRNA coordinates with chromatin organization in carcinogenesis. Nucleosome formation involves DNA wrapping around structural histone proteins, which are organized into chromatin. Gene regulation is directly influenced by chromatin organization, which includes the accessible/active euchromatin and condensed/suppressed heterochromatin (83). Chromatin and its regulatory elements are widely distributed in cancer genomes. Previous research has highlighted the importance of chromatin TAD structure in interacting with structural/regulatory protein complexes and lncRNAs (84) (Fig. 3A). CTCF is a key regulator of mammalian 3D genome organization (10). The CTCF/cohesin complex is responsible for modulating chromatin TAD boundaries, as well as enhancer-promoter long-range contacts within TADs to regulate gene expression in cancer genomes (11,85). Additionally, the SWItch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex

serves a critical regulatory role in the development and progression of various types of cancer (86).

Recent research has demonstrated lncRNA *Xist* mediates X-chromosome inactivation by forming 3D genome architecture (87,88). It recruits PRC2 to deposit H3K27me3 and interacts with CTCF to mediate long-range chromosomal interactions (89,90). In addition, posterior *HOXA* locus-associated lncRNA *HOTTIP* activates posterior *HOXA* genes and the canonical Wnt/ β -catenin pathway, promoting aberrant posterior *HOXA* TADs and chromatin signature in development of AML (91). The abnormal expression of *HOTTIP* in leukemic cells enhances self-renewal of LSCs, ultimately leading to leukemic transformation of hematopoietic stem cells through its binding to leukemic-specific transcriptional factors or CTCF motifs (18,49) (Fig. 3B). lncRNA *HOXBLINC* recruits the MLL1/Setd1a complex to deposit H3K4me3 on anterior *HoxB* genes and coordinates with CTCF-mediated chromatin loops, enhancing LSC survival in AML (50,92,93). Furthermore, lncRNA *H19* regulates chromatin organization by recruiting CTCF to unmethylated differentially methylated regions, suppressing insulin-like growth factor 2 (IGF2) and preventing FoxO3-mediated cell cycle arrest (94). Nuclear-retained lncRNA *Firre* modulates the 3D arrangement of the genome and localizes at chromatin both in *cis* and *trans* to form a distinct nuclear compartment in cancer (95,96). Collectively, lncRNAs are essential for mediating oncogenic TADs that lead to carcinogenesis by recruitment of structural/regulatory protein complexes, including CTCF and cohesin complex (Table SI).

Recent studies have underscored the key role of lncRNAs in chromatin remodeling and gene transcription in carcinogenesis (97-99). Tang *et al* (88) demonstrated that lncRNAs

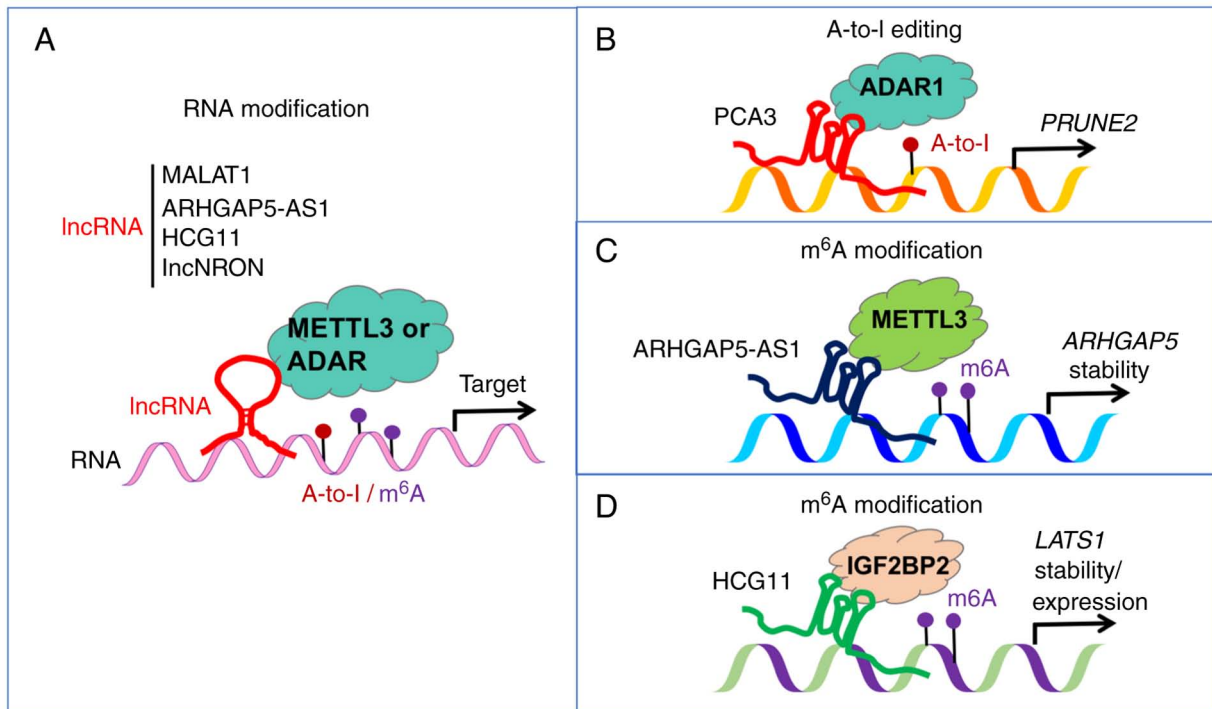


Figure 4. lncRNAs recruit RNA-modifying regulators to mediate gene expression in cancer genome. (A) lncRNAs directly recruit RNA-modifying regulators to mediate RNA methylation and A-to-I RNA editing in cancer. (B) lncRNA *PCA3* recruits ADAR1 enzyme to mediate A-to-I modification of *PRUNE2*, regulating its gene expression in development of prostate cancer. (C) lncRNA *ARHGAP5-AS1* recruits METTL3 complex to regulate *ARHGAP5* stability and expression in gastric cancer. (D) lncRNA *HCG11* recruits IGF2BP2 to regulate *LATS1* stability and expression in lung adenocarcinoma. lnc (long non-coding); A-to-I (Adenosine-to-inosine); PRUNE2 (Prune Homolog 2 With BCH Domain); METTL (Methyltransferase-Like); ARHGAP5 (Rho GTPase Activating Protein 5); IGF2BP2 (Insulin-like growth factor 2 mRNA-binding protein 2); LATS1 (large tumor suppressor kinase 1); ADAR (adenosine deaminase acting on RNA); m⁶A (N6-methyladenosine).

play a crucial role in recruiting imitation SWI/SNF family proteins to specific genomic regions, thereby activating the transcription of target genes in carcinogenesis. lncRNA *UCA1* interacts with Brahma-related gene 1 (BRG1) of the chromatin SWI/SNF remodeling complex to hinder its binding to *p21* promoter locus, promoting gallbladder cancer (100). Moreover, lncRNA *MALAT1* is essential for forming a complex with the chromatin remodeling component BRG1, epigenetically promoting inflammation-related hepatocellular carcinoma progression (101,102) (Fig. 3C). lncRNA nuclear enriched transcript 1 (*NEAT1*) interacts with the subunit AT rich interactive domain 1B of the BRM-associated factor)-type SWI/SNF complex through the formation of paraspeckles (nuclear bodies) in tumorigenesis (97). *NEAT1* regulates nuclear paraspeckle assembly by the recruitment of the subunit of SWI/SNF complex component BRG1 in colorectal cancer cells (103,104). lncRNA *LncTCF7* has been shown to enhance the activation of the *TCF7* transcriptional promoter and the WNT signaling pathway by recruiting SWI/SNF complex, thereby increasing stemness of cancer cells (105,106). lncRNA *SCHLAPI* promotes aggressive prostate cancer invasion and metastasis by interacting with and antagonizing SWI/SNF complex (107,108).

In summary, lncRNAs interact with chromatin organization regulators to regulate gene expression in cancer cells. Mechanistically, lncRNAs such as *MALAT1*, *LncTCF7* and *SCHLAPI* interact with chromatin remodeling complexes to influence chromatin structure and accessibility. *HOTTIP* recruits CTCF/cohesin to activate oncogenic TADs in AML,

while *MALAT1* and *LncTCF7* coordinate with SWI/SNF to promote hepatocellular and colorectal cancer, respectively. Therefore, lncRNAs serve key roles in modulating chromatin organization by interacting with CTCF/cohesin complex or ISWI/SNF family proteins to promote transcription of oncogenes in cancer development and progression (Fig. 3A-D; Table SI).

3. lncRNAs mediate epitranscriptomic modification in carcinogenesis

RNA modifications, including methylation and RNA editing, are key for various cellular processes in cancer cells, including RNA stability, structure and metabolism, localization and translation (109). lncRNAs play key roles in carcinogenesis by recruiting RNA modification complexes at the specific gene loci. lncRNAs directly interact with RNA modification complexes, such as RNA methyltransferases and editing enzymes, to modulate RNA modification and gene expression in cancer genomes (Fig. 4A) (110-116). By serving as molecular guides or scaffolds, lncRNAs directly recruit RNA modifiers to target RNAs, thereby influencing RNA modification patterns and driving cancer progression.

lncRNA *HIF1A-AS2* directly recruits the ADAR (adenosine deaminase RNA specific) enzyme to facilitate ADAR1-dependent A-to-I editing, driving breast cancer progression and metastasis (117,118). Similarly, lncRNA prostate cancer antigen 3 (*PCA3*) binds to ADAR enzyme, promoting A-to-I editing of *PRUNE2* pre-mRNA and

regulating expression of the tumor suppressor gene *PRUNE2*, thereby contributing to the development of prostate cancer (119) (Fig. 4B). Additionally, the expression of lncRNA *LINC00944* is associated with ADAR1 levels and mediates ADAR interactions with Dicer or Staufen protein, linked to poor survival in breast cancer (110). Consequently, lncRNAs impact expression of their target RNAs and contribute to tumorigenesis by interacting with the RNA A-to-I editing modifier ADAR (Table SI).

lncRNA *MALAT1* recruits methyltransferase-like 3 (*METTL3*) to induce m⁶A modification of *miR-26b*, promoting epithelial-mesenchymal transition and metastasis via the *MALAT1/miR-26b/HMGA2* (high mobility group AT-hook 2 (*HMGA2*)) axis in breast cancer (120,121). Additionally, lncRNA *AI662270* enhances CTGF (Connective tissue growth factor) expression post-transcriptionally by recruiting *METTL3* to the *CTGF* promoter and inducing m⁶A modifications on the nascent mRNA in carcinogenesis (111). Moreover, lncRNA *ARHGAP5-AS1* recruits the *METTL3* enzyme to mediate m⁶A methylation of *ARHGAP5*, thereby stabilizing this gene in the cytoplasm and conferring chemo-resistance in gastric cancer (115) (Fig. 4C). Another oncogenic lncRNA, *LNC942*, interacts with the *METTL14* enzyme to stabilize downstream oncogene expression, promoting cancer cell proliferation and progression (122).

Recent studies have revealed interactions between lncRNAs and m⁶A recognition proteins, such as YTHDC1 (YTH domain containing 1) (123), YTHDF2 (YTH Domain Family 2) (124) and ALKBH5 (AlkB Homolog 5) (113), regulate cellular processes associated with cancer development. For example, lncRNA *HCG11* recruits m⁶A recognition protein IGF2BP2 (IGF2 mRNA binding protein 2) to stabilize *LATS1* (Large tumor suppressor homolog 1) mRNA, enhancing *LATS1* expression in lung adenocarcinoma (116) (Fig. 4D). lncRNA *MALAT1* interacts with m⁶A recognition protein YTHDC1 to regulate nuclear speckle composition and oncogene expression in carcinogenesis (125). lncRNA-*CBSLR* recruits m⁶A recognition protein YTHDF2 to form the *CBSLR* (CBS mRNA Stabilizing lncRNA)/YTHDF2/CBS (cystathionine-beta-synthase) complex which decreases CBS mRNA stability in an m⁶A modification-dependent manner in gastric cancer (126). lncRNA *lncNRON* recruits the m⁶A eraser ALKBH5 demethylase to decrease *Nanog* m⁶A methylation, inhibiting *Nanog* mRNA decay in gastric cancer (127). Additionally, anti-sense lncRNA *FOXMI-AS* recruits the m⁶A eraser ALKBH5 to decrease m⁶A abundance on sense mRNA, leading to activation of downstream targets in glioblastoma stem-like cells (128). Moreover, studies have demonstrated lncRNA *KB-1980E6.3*, associated with hypoxia, recruits the m⁶A reader IGF2BP1 to stabilize *c-Myc* mRNA, thereby maintaining breast cancer stem cell stemness (129,130) (Fig. 4A-D; Table SI).

In summary, studies have highlighted the role of lncRNAs in mediating epitranscriptomic modifications, which are reversible chemical modifications on RNA molecules that impact oncogene expression and carcinogenesis (15,131,132). The interplay between lncRNAs and epitranscriptomic modification regulators in carcinogenesis underscores the complexity of regulatory networks that control oncogene expression in cancer (15). Some specific lncRNAs, such as *MALAT1*, *ARHGAP5-AS1* and *lncNRON*, have been implicated

in carcinogenesis by recruiting *METTL3/METTL14* or *ALKBH5* enzymes. Additionally, lncRNAs such as *HCG11*, *lncRNA-CBSLR* and *KB-1980E6.3* regulate oncogene expression by recruitment of m⁶A readers. lncRNAs play a direct role in recruiting RNA modification complexes, including RNA methyltransferases and RNA editing complexes, to regulate RNA modifications and abnormal oncogene expression, ultimately contributing to carcinogenesis (Figs. 1-4; Table SI). Collectively, these findings underscore the diverse and complex regulatory roles that lncRNAs serve in mediating m⁶A modification and gene expression in various types of cancer, highlighting their potential as therapeutic targets for cancer treatment.

4. lncRNAs as diagnostic and prognostic markers in cancer

lncRNAs are key regulators of cancer biology, operating through both epigenetic and epitranscriptomic mechanisms (17,133,134). As epigenetic regulators, lncRNAs interact with chromatin-modifying complexes (such as polycomb repressors and DNA methyltransferases) to silence tumor suppressor genes or activate oncogenes (131,135). In their epitranscriptomic capacity, lncRNAs orchestrate RNA modification (such as m⁶A methylation and A-to-I editing) to stabilize oncogenic transcripts or enhance their translational efficiency (132). These dual regulatory roles establish lncRNAs as master regulators of cancer hallmarks, including proliferation, metastasis and therapy resistance. Beyond their mechanistic roles, lncRNAs are as critical diagnostic and prognostic biomarkers in carcinogenesis. Their tissue- and cancer-specific expression profiles, combined with their ability to regulate key oncogenic pathways (such as those controlling proliferation, apoptosis and metastasis), position them as promising tools for early cancer detection, risk stratification and personalized therapeutic strategies (136).

Advancements in transcriptome sequencing data availability may facilitate the discovery of lncRNA biomarkers. *HOX* family genes, such as *HOTAIR*, *HOXBLINEC* and *HOTTIP*, are frequently upregulated in cancer and closely linked to carcinogenesis (18,59,61,92). Utilizing *HOTAIR* measurement for risk stratification of patients undergoing surgery may enhance precision medicine strategies for aggressive esophageal cancer (27). Mechanistically, *HOTAIR* influences the expression of the *MTHFR* gene by recruiting DNMT3s to the *MTHFR* gene promoter, resulting in esophageal cancer chemoresistance (27) (Fig. 1B). The function of *HOTAIR* lncRNA may be context- or cell-type-specific, but it still serves as a valuable clinical prognostic indicator. In patients with metastatic AML, high levels of *HOTTIP* expression are associated with shorter overall survival and increased responsiveness to WNT inhibitor ICG-001 treatment compared with those with low levels (18). Mechanistically, *HOTTIP* regulates *HOXA9* oncogene expression and the WNT/ β -Catenin signaling pathway, influencing AML development and progression (18) (Fig. 2B). In addition, *HOTTIP* coordinates with CTCF in mediating R-loops and TAD formation at crucial hematopoietic/leukemogenic loci to regulate expression of leukemia-related genes in AML leukemogenesis (91) (Fig. 3B). *HOXBLINEC* expression is associated with poor prognosis in AML based on The Cancer Genome Atlas

datasets (50) (Fig. 2C). *HOXBLINE* shows the highest levels of elevated expression in patients with AML with disease progression compared with patients without progression, suggesting its potential as a reliable biomarker with cancer- or tissue-specific expression profiles in AML.

Aberrant expression of lncRNAs and their involvement in cellular processes establish them as promising therapeutic targets for cancer. Studies have highlighted the importance of elucidating lncRNA-mediated mechanisms in cancer development and metastasis (59,77,125,137). For example, inhibitors targeting *LINC01212* have efficacy in melanoma treatment (138). *lncMyoD* has been identified as a functional regulator of IMP1 (IGF2 mRNA-binding protein (IMP)1 and IMP2, highlighting its therapeutic potential in sarcoma (139). Additionally, *lncRNA-6585* and its associated antibody are under investigation for cervical cancer diagnosis and therapy (138). Emerging strategies, such as nanomaterials-based technologies, represent cutting-edge approaches for targeting lncRNAs in cancer therapy (140). These innovations, including nanoparticle delivery systems, enhance specificity and efficacy of RNA-based therapies (140). A recent study systematically summarized advances in targeting the lncRNA-Wnt axis with flavonoids for colorectal cancer (CRC) therapy, underscoring the potential of flavonoid-based strategies to exploit epigenetic mechanisms for CRC prevention and treatment (141).

lncRNAs are increasingly leveraged in nucleic acid-based therapeutics in cancer, including CRISPR/Cas9 (Clustered regularly interspaced short palindromic repeats associated protein 9) sgRNA design, small interfering RNA (siRNA) and antisense oligonucleotides (ASOs) (142). For example, CRISPR/Cas9 sgRNA-mediated silencing of *UCA1*, *NEAT1* or *MALAT1* inhibits cancer cell metastasis (70,143). *MALAT1* serves as a druggable lncRNA for precision anti-cancer strategies, while microRNAs and lncRNAs represent promising targets in drug development (70,144). Furthermore, siRNA and ASOs enable precise gene silencing, making them key tools for research and clinical applications (143,144). For example, siRNA targeting DDX11 antisense RNA 1) has been developed for liver cancer therapy (145). In a luminal mouse mammary tumor virus-PyMT mouse mammary carcinoma model, promoter depletion or ASO-mediated knockdown of *MALAT1* notably decreases lung cancer metastasis (120).

Collectively, lncRNAs are associated with cancer development and progression, underscoring their potential as prognostic and predictive biomarkers. Their cancer- or tissue-specific expression profiles across malignancies highlight their clinical relevance. The integration of lncRNAs into clinical oncology signifies a new era of precision medicine. Their dual use as diagnostic/prognostic markers and therapeutic targets may transform cancer management by enabling earlier detection, personalized treatment and dynamic monitoring. As research advances, lncRNAs are poised to transition from experimental discoveries to key assets in treating cancer, offering now avenues for improving patient outcomes.

5. Conclusion

The aberrant expression of lncRNAs is associated with poor prognosis of patients with cancer. Understanding the mechanisms by which lncRNAs drive cancer progression is

key for developing effective therapy (146). lncRNAs possess structural versatility, enabling them to recruit epigenetic and epitranscriptomic regulators, including PRC1, PRC2, LSD1, MLL, DNMTs, CTCF, cohesin, METTL3 and ALKBH5. By interacting with these regulators, lncRNAs modulate the epigenome and amplify oncogenic pathways in carcinogenesis (147,148). Therefore, future studies may elucidate the interlocking functions of lncRNAs with epigenetic or epitranscriptomic regulators to develop new cancer therapies and earlier prognosis strategies (46).

Dysregulation of lncRNA-mediated DNA modification is implicated in tumor initiation, progression and metastasis (27). Understanding crosstalk between lncRNAs and DNA modification in cancer is crucial for investigating underlying molecular mechanisms of tumorigenesis. Aberrant DNA 5mC methylation patterns, such as hypermethylation of tumor suppressor genes and hypomethylation of oncogenes, are implicated in cancer development and progression. lncRNAs recruit DNMTs complex to the specific genomic loci, leading to changes in DNA methylation patterns and oncogene expression during carcinogenesis (26,27). For example, lncRNA *HOTAIR* recruits DNMT3A/3B complex to the promoter regions of tumor suppressor gene *MTHFR*, promoting cancer cell proliferation and metastasis (27). Moreover, *HOTAIR* epigenetically suppresses the *miR-122* expression via DNMTs-mediated DNA methylation, contributing to hepatocarcinogenesis (149). Additionally, lncRNAs, such as *HAGLR*, *CCDC26* and *TTY15*, have been implicated in recruiting DNMTs to influence the DNA methylation of their targets in cancer cells (33-35). Overall, recruitment of DNMTs by lncRNAs represents the epigenetic mechanism by which lncRNAs regulate oncogene expression in carcinogenesis (Fig. 1A-D). Although numerous lncRNAs can influence the DNA methylation of their targets leading to carcinogenesis, it is unknown which regulators are recruited by lncRNA in cancer. Further studies should explore the epigenetic mechanisms of lncRNA-mediated DNA modification in cancer genome.

The recruitment of histone modification complexes by lncRNAs serves a crucial role in the regulation of gene expression patterns associated with cancer development and progression. lncRNAs recruit HAT complexes to specific genomic loci, resulting in changes in histone acetylation patterns during carcinogenesis (59,60). This recruitment of histone modifying regulators by lncRNAs regulates changes in gene expression patterns associated with cancer cell proliferation, invasion, metastasis, apoptosis, cell cycle progression and drug resistance (Fig. 5). For example, lncRNA *HOTAIR* interacts with the HAT complex PRC2 to increase H3K27me3 at oncogene promoters and subsequently silence their expression (59-61) (Fig. 2A-B). Additionally, *HOTAIR* and *Air* interact with PRC2 complex or G9a to regulate histone acetylation or methylation at specific gene loci, promoting tumorigenesis (51,59-61). Furthermore, oncogenic lncRNAs *HOTTIP*, *HOXBLINE*, *MIAT*, *LAMP5-AS1*, *ANRIL*, *CircAGFG1*, *PANDA* and *LINPI*, directly interact with MLL, DOT1L, SETD1A and EZH2, influencing cancer cell proliferation, cell cycle progression and apoptosis (Fig. 5). lncRNA *AGAP2-AS1* directly binds CBP/P300 to mediate the H3K27 acetylation at the promoter of the carcinogenic protein MyD88, leading to chemoresistance in breast cancer (82) (Figs. 2D and 5).

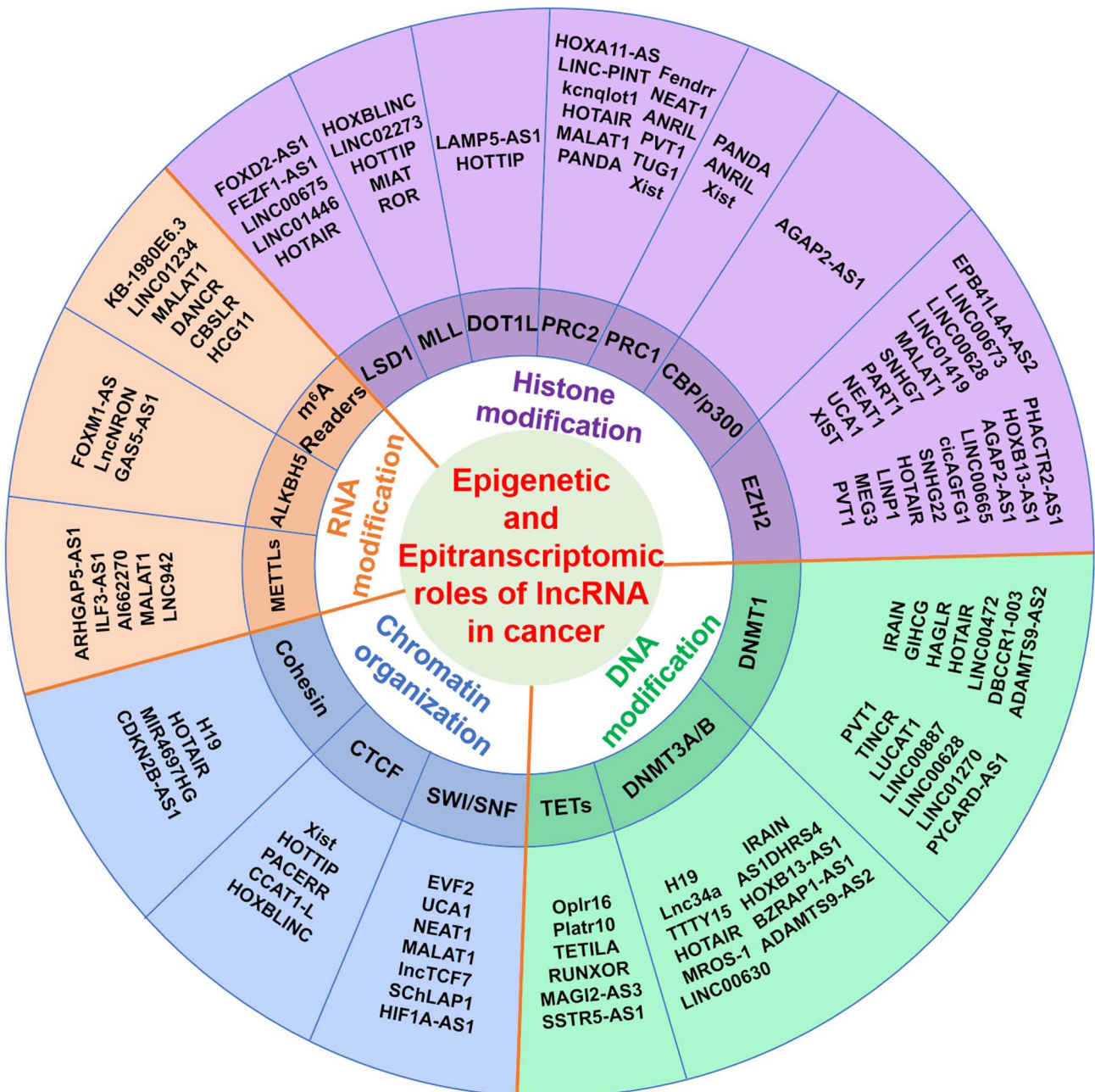


Figure 5. Epigenetic and epitranscriptomic roles of lncRNAs in cancer. lncRNAs serve key roles in recruiting epigenetic and epitranscriptomic regulators, including DNA- and histone-modifying enzymes, RNA-modifying regulators and chromatin organization-associated proteins. This recruitment leads to dysregulated gene expression, contributing to cancer development and progression. Inc, long non-coding.

While the role of lncRNA-mediated histone modification in carcinogenesis is well-established (18,50,51,53,55,69), further research is needed to understand how lncRNAs recruit histone modification complexes. The present review provides an overview of the current understanding of how lncRNAs mediate the recruitment of histone modification complexes in carcinogenesis, emphasizing the potential of targeting lncRNA-histone modifier interactions as a therapeutic approach for cancer treatment (Fig. 5).

RNA modifications, such as m6A methylation and A-to-I editing, influence mRNA stability, translation and splicing. Dysregulation of m6A methylation is implicated in various cancers. lncRNAs recruit the METTL3/METTL14 complex to mediate m6A methylation, regulating target gene expression

and driving tumor growth and metastasis (150,151). lncRNA *MALAT1* recruits the METTL3/METTL14 complex to promote methylation and subsequent translation at specific mRNAs, enhancing NSCLC cell proliferation and invasion (112). lncRNAs recruit m6A readers and eraser to mediate oncogene expression or inactivate tumor suppressive genes in carcinogenesis, such as IGF2BP1, IGF2BP2, YTHDC1, YTHDF2 and ALKBH5 (116,125,126,128,129). Additionally, ADAR1-dependent A-to-I editing serves a critical role in the progression and metastasis of cancers (117,118). lncRNAs *PCA3* and *LINC00944* recruit ADAR to regulate the expression of the tumor-related genes in carcinogenesis (110,119) (Fig. 4A-D). Overall, the recruitment of the RNA A-to-I editing enzyme, METTL3/METTL14 complex and m6A or

m⁶A readers by lncRNAs represents a novel epitranscriptomic mechanism by which lncRNAs modulate oncogene expression driving carcinogenesis.

In addition, lncRNAs serve essential roles in 3D chromatin organization by recruiting, bridging, and guiding the CTCF/cohesin complex to specific genomic regions. Depletion of RBRs disrupts CTCF-mediated DNA recognition and binding and chromatin loops in cancer genome (12). Thus, lncRNAs coordinate with CTCF, contributing to the genome topological regulation via the RNA-dependent mechanism. lncRNA *HOTTIP* coordinates with CTCF to mediate TAD formation at key hematopoietic/leukemogenic loci for AML development and progression (18) (Fig. 3B). lncRNA *HOTTIP* also cooperates with CTCF/cohesin-mediated TAD structure in LSC regulation and AML leukemogenesis according to its function in specific leukemic genome topology (91) (Fig. 3B). These findings suggest that lncRNAs contribute to genome topological regulation via RNA-dependent mechanisms. Further research is needed to explore the roles of architectural RNAs and regulatory lncRNAs in CTCF/cohesin-mediated chromatin organization across numerous types of cancer.

lncRNAs serve physiological and pathological roles in numerous aspects of genome function and biological processes, such as cell development, differentiation, proliferation, invasion and migration. Unlike protein-coding genes, lncRNAs lack well-defined domains, making their regulatory mechanisms diverse and complex (152). Notably, lncRNAs >300 bp contain multiple functional domains that interact with various factors to coordinate activity in both time and space (153). For example, *HOTTIP* cooperates with WDR5/MLL/DOT1L, a large family of RNA-binding proteins involved in cellular processes such as alternative splicing, mRNA stability and transcriptional regulation (18). Furthermore, *HOTTIP* can bind to the RNA binding domains of CTCF/cohesin, leading to aberrant induction of oncogene expression and the WNT pathway in leukemogenesis (91). lncRNA *HOTTIP* mediates histone modification and chromatin organization to regulate *HOXA* oncogene expression and WNT signaling pathways by recruiting modifiers, including WDR5/MLL/DOT1L and CTCF/cohesin. The 3,343 bp lncRNA *HOTTIP* contains different functional domains that can recruit different DNA or RNA modifying regulators. Experimental frameworks for studying the cis- and trans-acting functions of this lncRNA have been detailed in previous research (18,91). Similarly, upregulation of *MALAT1* lncRNA in various types of cancer, along with its pleiotropic roles in gene regulation, has made it a target for therapeutic interventions in cancer (70). lncRNA *MALAT1* suppresses *E-cadherin* expression, promoting OS metastasis by recruitment of the PRC2 member EZH2 (69). lncRNA *MALAT1* also plays a key role in chromatin remodeling to promote inflammation-associated hepatocellular carcinoma progression by interaction with BRG1 (101,102). Additionally, *MALAT1* regulates the expression of *miR-26b* by recruiting METTL3, leading to the invasive and metastatic behavior of breast cancer via the *MALAT1/miR-26b/HMGA2* axis (120,121). These examples illustrate how lncRNAs with multiple functional domains interact with diverse modifiers to regulate cancer progression. While experimental

studies have provided insight into lncRNA functions, further research is needed to clarify their regulatory mechanisms across numerous types of cancer.

Previous studies have challenged traditional views of lncRNA function, highlighting their key roles in cancer development (154,155). Advances in RNA-associated technologies, such as ChIRP-seq (chromatin isolation by RNA purification sequencing), ChIRP-Mass Spectrometry, and iDRiP (identification of direct RNA interacting proteins), have enabled identification of lncRNAs that interact with DNA-modifying enzymes, histone modifiers, RNA-modifying complexes and chromatin-organizing proteins (156-158). Moreover, a deep understanding of lncRNA-driven epigenetic and epitranscriptomic regulation through next-generation sequencing technology strengthen its association with carcinogenesis (84). The regulation of lncRNAs in human may lead to the discovery of promising targets for cancer therapeutics. This has spurred the rapid growth of epigenetic drug discovery, with drug-targeting epigenetic enzymes being tested in the clinic for the treatment of various types of human cancer (159-161). lncRNAs provide a platform for identifying epigenetic targets, enabling the development of epi-drugs to counteract aberrant epigenetic enzymes. lncRNA expression shows high specificity, as they are expressed at different developmental stages and in a cancer type-specific manner (162,163). Disrupting expression of a specific lncRNA associated with epigenetic regulation can lead to the upregulation of its target (6).

Understanding of how lncRNAs mediate epigenetic and epitranscriptomic regulators to control the cancer biological processes, such as invasion-metastasis, and influence the tumor microenvironment is steadily advancing (Fig. 5; Table SI). Critically, lncRNAs form relatively stable secondary and higher structures to facilitate cellular organization and gene regulation, including DNA replication, RNA transcription, protein translation and cell and cell differentiation (164,165). The complex structural features make lncRNAs potential players in epigenetic regulation in various types of cancer (96). Multiple pieces of evidence suggest that structural features of lncRNAs are essential for understanding their function and roles in cancer development and progression (7,15,29,33,69). In conclusion, the present review highlighted the role of lncRNA in mediating epigenetic and epitranscriptomic regulation to control oncogene expression. Directly recruiting DNA modifying complex, histone modifying regulators, chromatin organization associated regulators, and RNA modifying complex plays a role in carcinogenesis. Understanding lncRNA functions and structures is key for developing targeted cancer therapy.

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Authors' contributions

HL conceived the study and wrote and revised the manuscript. CD, HQ, RF and HY wrote the manuscript. AS and HL wrote, reviewed and edited the manuscript. CD, HQ, RF and HL constructed figures. HL supervised the study. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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