Epigenetic and epitranscriptomic role of lncRNA in carcinogenesis (Review)

CHUNFEI DAI[1,2*], HAOYUE QIANJIANG[1,2*], RUISHUANG FU[1], HUIMIN YANG[1], AIQIN SHI[3] and HUACHENG LUO[1]

[1]Zhejiang Cancer Hospital, The Key Laboratory of Zhejiang Province for Aptamers and Theranostics, Hangzhou Institute of Medicine, The Chinese Academy of Sciences, Hangzhou, Zhejiang 310022, P.R. China; [2]College of Pharmacy, Zhejiang University of Technology, Hangzhou, Zhejiang 310014, P.R. China; [3]Xianghu Laboratory, Hangzhou, Zhejiang 311231, P.R. China

Received December 24, 2024; Accepted February 13, 2025

DOI: 10.3892/ijo.2025.5735

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.

Contents

1. Introduction
2. lncRNA recruits epigenetic regulators contributing to carcinogenesis
3. lncRNAs mediate epitranscriptomic modification in carcinogenesis
4. lncRNAs as diagnostic and prognostic markers in cancer
5. Conclusion

Correspondence to: Professor Huacheng Luo, Zhejiang Cancer Hospital, The Key Laboratory of Zhejiang Province for Aptamers and Theranostics, Hangzhou Institute of Medicine, The Chinese Academy of Sciences, 150 Fucheng Road, Qiantang, Hangzhou, Zhejiang 310022, P.R. China
E-mail: luohuacheng@him.cas.cn

*Contributed equally

Key words: long non-coding RNA, chromatin modification, epigenetic regulation, epitranscriptomic regulation, carcinogenesis

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

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 (m^6A) 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* (methylenetetrahydrofolate 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 *TTTY15* 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 *AS1DHRS4* 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 *Oplr16* 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 *MAGI2-AS3* recruits TET2 to the *LRIG1* (leucine rich repeats and immunoglobulin

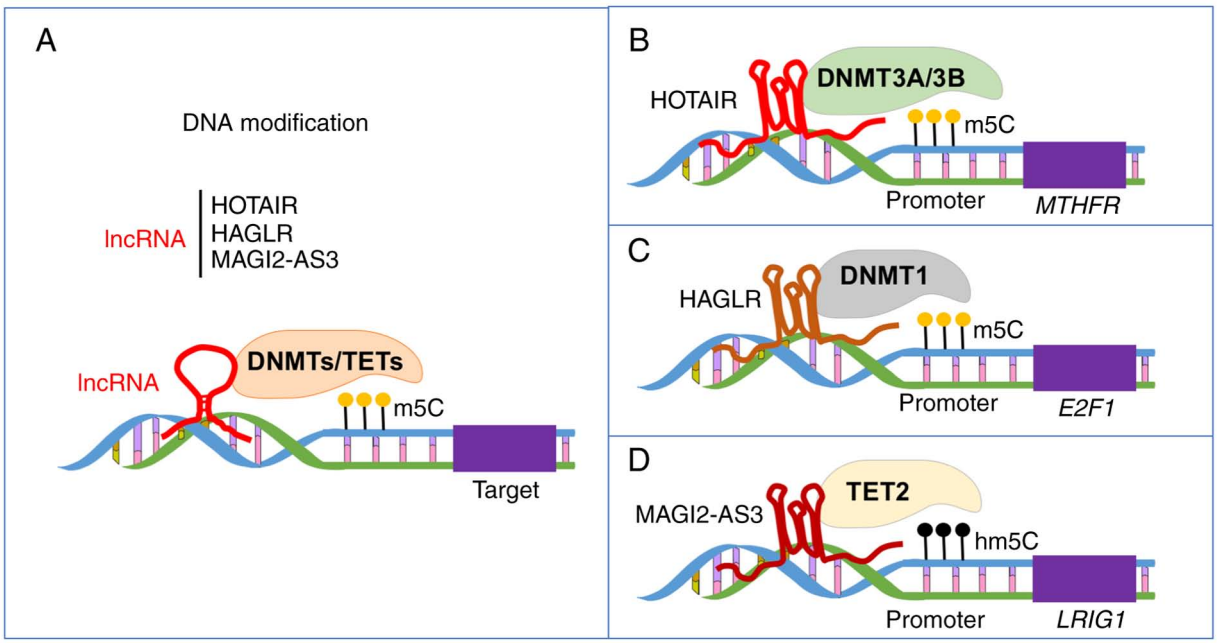

Figure 1. lncRNAs recruit DNA modifying regulators to modulate the expression of target genes in cancer genome. (A) In cancer, lncRNAs directly recruit DNMTs/TETs to induce DNA methylation or demethylation, respectively. (B) lncRNA *HOTAIR* directly recruits DNMT3A/3B modifying complex to regulate *MTHFR* 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. lnc (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 *HOXBLINC* 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*

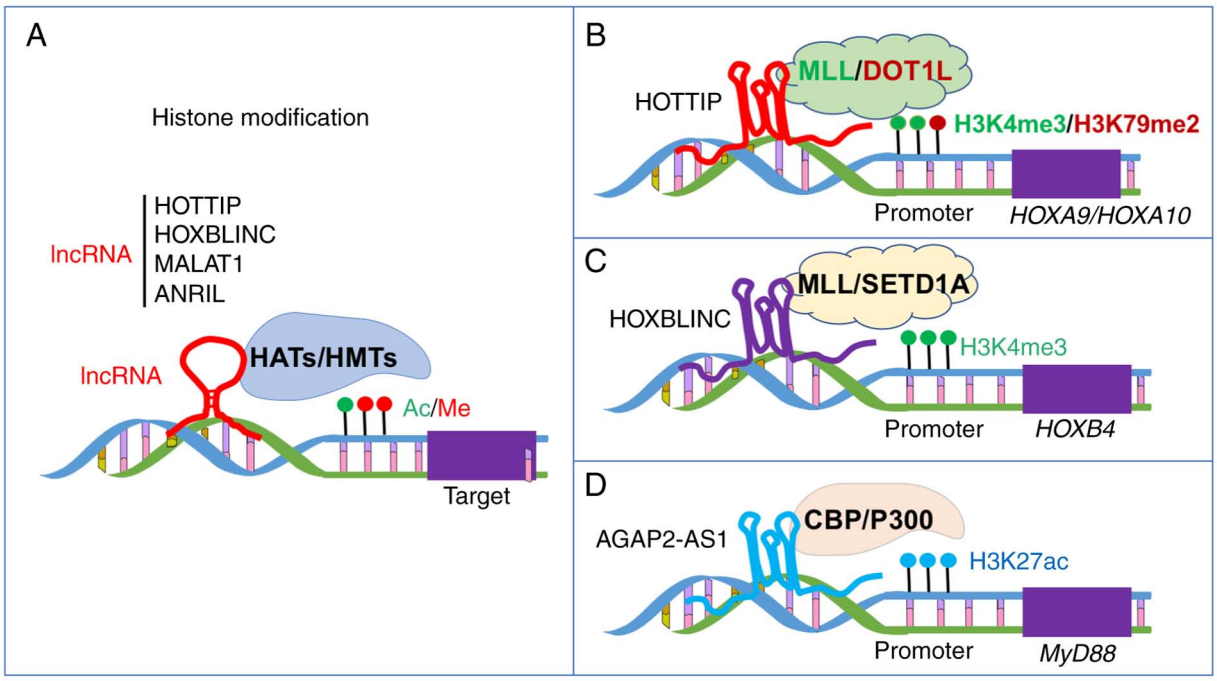

Figure 2. lncRNAs recruit histone modifying regulators to mediate gene expression in cancer genome. (A) lncRNAs directly recruit HMTs or HATs to mediate histone modification in cancer. (B) lncRNA *HOTTIP* recruits MLL/DOT1L complex to regulate *HOXA9* and *HOXA10* oncogene expression in AML leukemogenesis. (C) lncRNA *HOXBLINC* 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

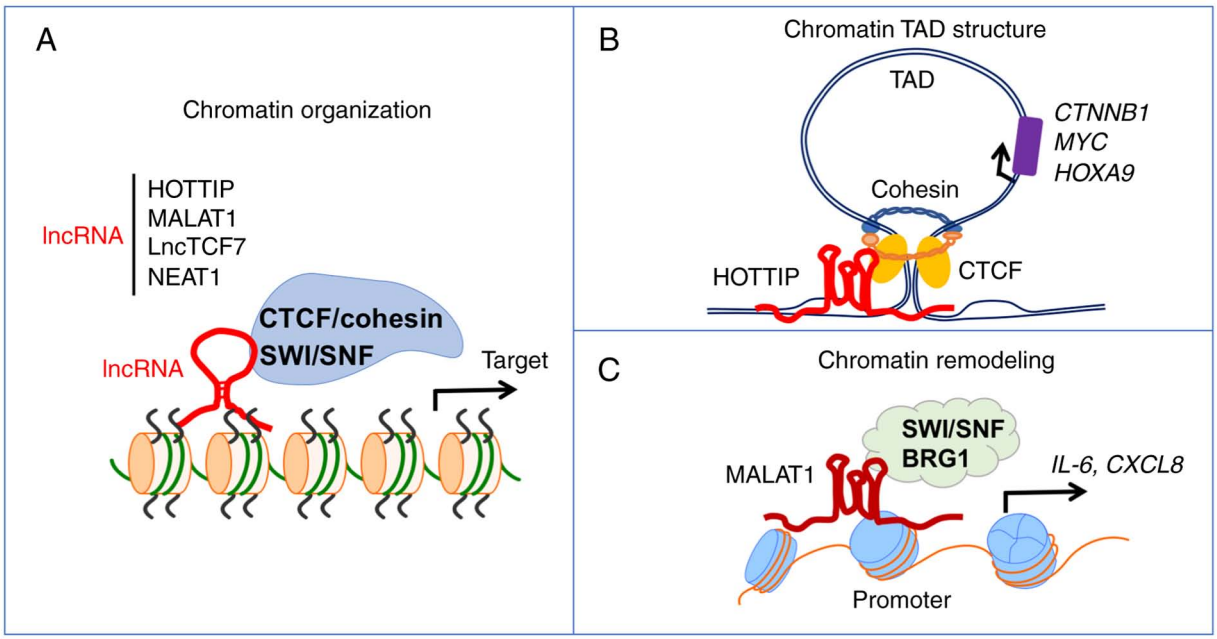

Figure 3. lncRNAs interact with chromatin organization-associated regulators to mediate gene expression in cancer. (A) lncRNAs directly recruit CTCF/cohesin or SWI/SNF complex to mediate chromatin organization and gene expression in cancer. (B) lncRNA *HOTTIP* interacts with CTCF/cohesin complex to regulate *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. lnc (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 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 leads 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

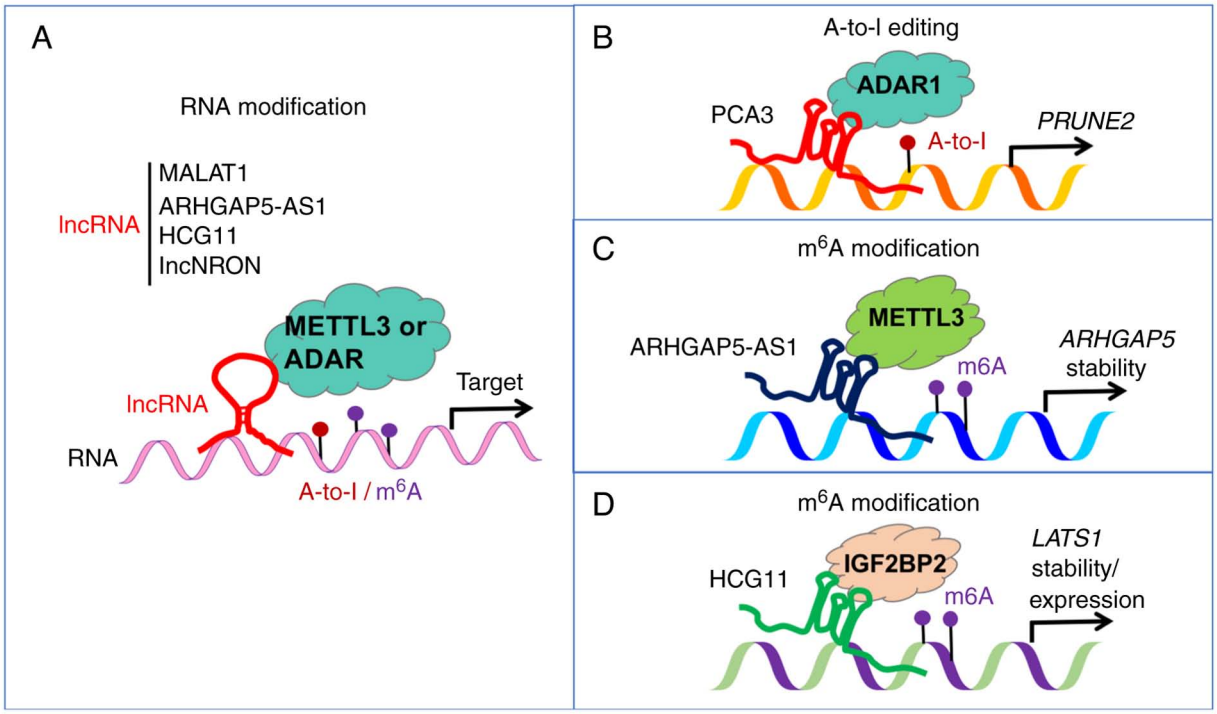

Figure 4. lncRNAs recruit RNA-modifying regulators to mediate gene expression in cancer genome. (A) lncRNAs directly recruit RNA-modifying regulators to mediate RNA methylation and A-to-I RNA editing in cancer. (B) lncRNA *PCA3* recruits ADAR1 enzyme to mediate A-to-I modification of *PRUNE2*, regulating 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); m^{6}A (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 *SCHLAP1* 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 *SCHLAP1* 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 m^{6}A 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 m^{6}A modifications on the nascent mRNA in carcinogenesis (111). Moreover, lncRNA *ARHGAP5-AS1* recruits the METTL3 enzyme to mediate m^{6}A 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 m^{6}A 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 m^{6}A 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 m^{6}A recognition protein YTHDC1 to regulate nuclear speckle composition and oncogene expression in carcinogenesis (125). *lncRNA-CBSLR* recruits m^{6}A recognition protein YTHDF2 to form the CBSLR (CBS MRNA Stabilizing LncRNA)/YTHDF2/CBS (cystathionine-beta-synthase) complex which decreases CBS mRNA stability in an m^{6}A modification-dependent manner in gastric cancer (126). lncRNA *lncNRON* recruits the m^{6}A eraser ALKHB5 demethylase to decrease *Nanog* m^{6}A methylation, inhibiting *Nanog* mRNA decay in gastric cancer (127). Additionally, anti-sense lncRNA *FOXM1-AS* recruits the m^{6}A eraser ALKBH5 to decrease m^{6}A 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 m^{6}A 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 m^{6}A 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 m^{6}A 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 m^{6}A 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*, *HOXBLINC* 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). *HOXBLINC* expression is associated with poor prognosis in AML based on The Cancer Genome Atlas

datasets (50) (Fig. 2C). *HOXBLINC* 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 *TTTY15,* 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*, *HOXBLINC*, *MIAT*, *LAMP5-AS1*, *ANRIL*, *CircAGFG1*, *PANDA* and *LINP1,* 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).

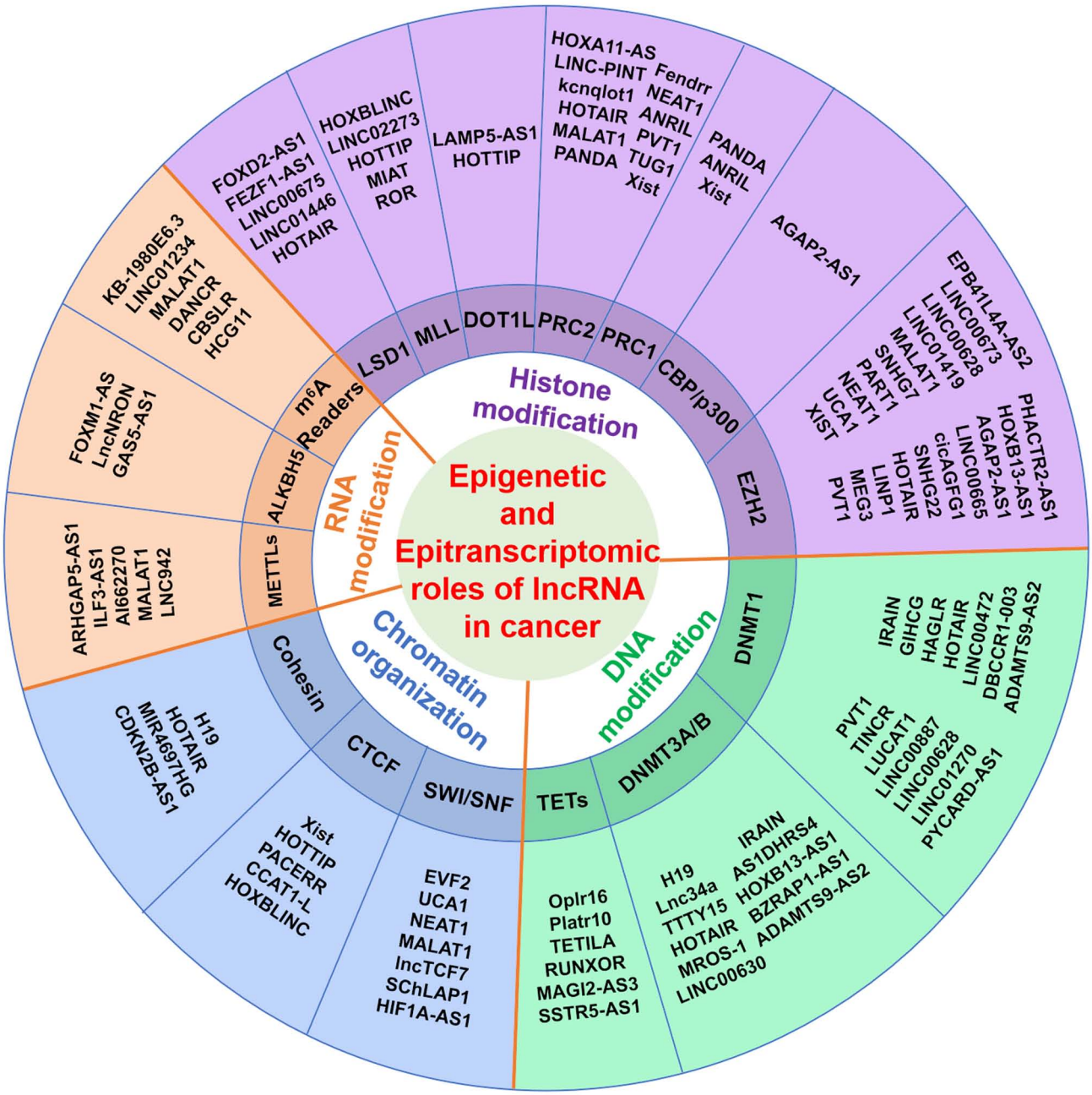

Figure 5. Epigenetic and epitranscriptomic roles of lncRNAs in cancer. lncRNAs serve key roles in recruiting epigenetic and epitranscriptomic regulators, including DNA- and histone-modifying enzymes, RNA-modifying regulators and chromatin organization-associated proteins. This recruitment leads to dysregulated gene expression, contributing to cancer development and progression. lnc, 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 m^6A 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 m^6A or

m^6A 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 epitranscritomic 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.

Acknowledgements

No applicable.

Funding

The present study was supported by National Natural Science Foundation of China (grant nos. 82270193 and 82470156) and Zhejiang Provincial Natural Science Foundation of China (grant no. YXD24H0801).

Availability of data and materials

Not applicable.

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.

References

1. Ransohoff JD, Wei Y and Khavari PA: The functions and unique features of long intergenic non-coding RNA. Nat Rev Mol Cell Biol 19: 143-157, 2018.
2. Djebali S, Davis CA, Merkel A, Dobin A, Lassmann T, Mortazavi A, Tanzer A, Lagarde J, Lin W, Schlesinger F, *et al*: Landscape of transcription in human cells. Nature 489: 101-108, 2012.
3. Wang D, Garcia-Bassets I, Benner C, Li W, Su X, Zhou Y, Qiu J, Liu W, Kaikkonen MU, Ohgi KA, *et al*: Reprogramming transcription by distinct classes of enhancers functionally defined by eRNA. Nature 474: 390-394, 2011.
4. Zhou Y, Sun W, Qin Z, Guo S, Kang Y, Zeng S and Yu L: LncRNA regulation: New frontiers in epigenetic solutions to drug chemoresistance. Biochem Pharmacol 189: 114228, 2021.
5. Morlando M and Fatica A: Alteration of epigenetic regulation by long noncoding RNAs in cancer. Int J Mol Sci 19: 570, 2018.
6. Khorkova O, Hsiao J and Wahlestedt C: Basic biology and therapeutic implications of lncRNA. Adv Drug Deliv Rev 87: 15-24, 2015.
7. Beckedorff FC, Amaral MS, Deocesano-Pereira C and Verjovski-Almeida S: Long non-coding RNAs and their implications in cancer epigenetics. Biosci Rep 33: e00061, 2013.
8. Lu Y, Chan YT, Tan HY, Li S, Wang N and Feng Y: Epigenetic regulation in human cancer: The potential role of epi-drug in cancer therapy. Mol Cancer 19: 79, 2020.
9. Tachiwana H, Yamamoto T and Saitoh N: Gene regulation by non-coding RNAs in the 3D genome architecture. Curr Opin Genet Dev 61: 69-74, 2020.
10. Phillips JE and Corces VG: CTCF: Master weaver of the genome. Cell 137: 1194-1211, 2009.
11. Fang C, Rao S, Crispino JD and Ntziachristos P: Determinants and role of chromatin organization in acute leukemia. Leukemia 34: 2561-2575, 2020.
12. Hansen AS, Hsieh TS, Cattoglio C, Pustova I, Saldaña-Meyer R, Reinberg D, Darzacq X and Tjian R: Distinct classes of chromatin loops revealed by deletion of an RNA-binding region in CTCF. Mol Cell 76: 395-411.e13, 2019.
13. Saldana-Meyer R, Rodriguez-Hernaez J, Escobar T, Nishana M, Jácome-López K, Nora EP, Bruneau BG, Tsirigos A, Furlan-Magaril M, Skok J and Reinberg D: RNA interactions are essential for CTCF-mediated genome organization. Mol Cell 76: 412-422, 2019.
14. Cui L, Ma R, Cai J, Guo C, Chen Z, Yao L, Wang Y, Fan R, Wang X and Shi Y: RNA modifications: Importance in immune cell biology and related diseases. Signal Transduct Target Ther 7: 334, 2022.
15. Dinescu S, Ignat S, Lazar AD, Constantin C, Neagu M and Costache M: Epitranscriptomic signatures in lncRNAs and their possible roles in cancer. Genes (Basel) 10: 52, 2019.
16. Yang Z, Xu F, Teschendorff AE, Zhao Y, Yao L, Li J and He Y: Insights into the role of long non-coding RNAs in DNA methylation mediated transcriptional regulation. Front Mol Biosci 9: 1067406, 2022.
17. Statello L, Guo CJ, Chen LL and Huarte M: Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol 22: 96-118, 2021.
18. Luo H, Zhu G, Xu J, Lai Q, Yan B, Guo Y, Fung TK, Zeisig BB, Cui Y, Zha J, *et al*: HOTTIP lncRNA promotes hematopoietic stem cell Self-renewal leading to AML-like disease in mice. Cancer Cell 36: 645-659.e8, 2019.
19. Greenberg MVC and Bourc'his D: The diverse roles of DNA methylation in mammalian development and disease. Nat Rev Mol Cell Biol 20: 590-607, 2019.
20. Zhao SG, Chen WS, Li H, Foye A, Zhang M, Sjöström M, Aggarwal R, Playdle D, Liao A, Alumkal JJ, *et al*: The DNA methylation landscape of advanced prostate cancer. Nat Genet 52: 778-789, 2020.
21. Robertson KD: DNA methylation, methyltransferases, and cancer. Oncogene 20: 3139-3155, 2001.
22. van der Velden PA, Metzelaar-Blok JA, Bergman W, Monique H, Hurks H, Frants RR, Gruis NA and Jager MJ: Promoter hypermethylation: A common cause of reduced p16(INK4a) expression in uveal melanoma. Cancer Res 61: 5303-5306, 2001.
23. Saif I, Bouziyane A, Benhessou M, Karroumi ME and Ennaji MM: Detection of hypermethylation BRCA1/2 gene promoter in breast tumours among Moroccan women. Mol Biol Rep 48: 7147-7152, 2021.
24. Wang Z, Yang B, Zhang M, Guo W, Wu Z, Wang Y, Jia L, Li S; Cancer Genome Atlas Research Network; Xie W and Yang D: lncRNA epigenetic landscape analysis identifies EPIC1 as an oncogenic lncRNA that interacts with MYC and promotes Cell-cycle progression in cancer. Cancer Cell 33: 706-720.e9, 2018.
25. Lyko F: The DNA methyltransferase family: A versatile toolkit for epigenetic regulation. Nat Rev Genet 19: 81-92, 2018.
26. Liu D, Wu K, Yang Y, Zhu D, Zhang C and Zhao S: Long noncoding RNA ADAMTS9-AS2 suppresses the progression of esophageal cancer by mediating CDH3 promoter methylation. Mol Carcinog 59: 32-44, 2020.
27. Zhang S, Zheng F, Zhang L, Huang Z, Huang X, Pan Z, Chen S, Xu C, Jiang Y, Gu S, *et al*: LncRNA HOTAIR-mediated MTHFR methylation inhibits 5-fluorouracil sensitivity in esophageal cancer cells. J Exp Clin Cancer Res 39: 131, 2020.
28. Wang L, Bu P, Ai Y, Srinivasan T, Chen HJ, Xiang K, Lipkin SM and Shen X: A long non-coding RNA targets microRNA miR-34a to regulate colon cancer stem cell asymmetric division. Elife 5: e14620, 2016.
29. Lai IL, Chang YS, Chan WL Lee YT, Yen JC, Yang CA, Hung SY and Chang JG: Male-specific long noncoding RNA TTTY15 inhibits Non-small cell lung cancer proliferation and metastasis via TBX4. Int J Mol Sci 20: 3473, 2019.
30. Li Q, Su Z, Xu X, Liu G, Song X, Wang R, Sui X, Liu T, Chang X, Huang D, *et al*: AS1DHRS4, a head-to-head natural antisense transcript, silences the DHRS4 gene cluster in cis and trans. Proc Natl Acad Sci USA 109: 14110-14115, 2012.
31. Su SC, Yeh CM, Lin CW, Hsieh YH, Chuang CY, Tang CH, Lee YC and Yang SF: A novel melatonin-regulated lncRNA suppresses TPA-induced oral cancer cell motility through replenishing PRUNE2 expression. J Pineal Res 71: e12760, 2021.
32. Li Y, Luo Q, Li Z, Wang Y, Zhu C, Li T and Li X: Long Non-coding RNA IRAIN inhibits VEGFA expression via enhancing Its DNA methylation leading to tumor suppression in renal carcinoma. Front Oncol 10: 1082, 2020.
33. Guo X, Chen Z, Zhao L, Cheng D, Song W and Zhang X: Long non-coding RNA-HAGLR suppressed tumor growth of lung adenocarcinoma through epigenetically silencing E2F1. Exp Cell Res 382: 111461, 2019.
34. Yoon JH, You BH, Park CH, Kim YJ, Nam JW and Lee SK: The long noncoding RNA LUCAT1 promotes tumorigenesis by controlling ubiquitination and stability of DNA methyltransferase 1 in esophageal squamous cell carcinoma. Cancer Lett 417: 47-57, 2018.
35. Jones R, Wijesinghe S, Wilson C, Halsall J, Liloglou T and Kanhere A: A long intergenic non-coding RNA regulates nuclear localization of DNA methyl transferase-1. iScience 24: 102273, 2021.

36. Xu X, Lou Y, Tang J, Teng Y, Zhang Z, Yin Y, Zhuo H and Tan Z: The long non-coding RNA Linc-GALH promotes hepatocellular carcinoma metastasis via epigenetically regulating Gankyrin. Cell Death Dis 10: 86, 2019.
37. Vennin C, Spruyt N, Robin YM, Chassat T, Le Bourhis X and Adriaenssens E: The long non-coding RNA 91H increases aggressive phenotype of breast cancer cells and up-regulates H19/IGF2 expression through epigenetic modifications. Cancer Lett 385: 198-206, 2017.
38. Jin L, Cai Q, Wang S, Wang S, Wang J and Quan Z: Long noncoding RNA PVT1 promoted gallbladder cancer proliferation by epigenetically suppressing miR-18b-5p via DNA methylation. Cell Death Dis 11: 871, 2020.
39. Wu X and Zhang Y: TET-mediated active DNA demethylation: Mechanism, function and beyond. Nat Rev Genet 18: 517-534, 2017.
40. Rasmussen KD and Helin K: Role of TET enzymes in DNA methylation, development, and cancer. Genes Dev 30: 733-750, 2016.
41. Al-Imam MJ, Hussein UA, Sead FF, Faqri AMA, Mekkey SM, Khazel AJ and Almashhadani HA: The interactions between DNA methylation machinery and long non-coding RNAs in tumor progression and drug resistance. DNA Repair (Amst) 128: 103526, 2023.
42. Zhou L, Ren M, Zeng T, Wang W, Wang X, Hu M, Su S, Sun K, Wang C, Liu J, *et al*: TET2-interacting long noncoding RNA promotes active DNA demethylation of the MMP-9 promoter in diabetic wound healing. Cell Death Dis 10: 813, 2019.
43. Roessner A, Franke S, Schreier J, Ullmann S, Karras F and Jechorek D: Genetics and epigenetics in conventional chondrosarcoma with focus on non-coding RNAs. Pathol Res Pract 239: 154172, 2022.
44. Zhu X, Du J, Yu J, Guo R, Feng Y, Qiao L, Xu Z, Yang F, Zhong G, Liu F, *et al*: LncRNA NKILA regulates endothelium inflammation by controlling a NF-κB/KLF4 positive feedback loop. J Mol Cell Cardiol 126: 60-69, 2019.
45. Liu B, Sun L, Liu Q, Gong C, Yao Y, Lv X, Lin L, Yao H, Su F, Li D, *et al*: A cytoplasmic NF-kappaB interacting long noncoding RNA blocks IkappaB phosphorylation and suppresses breast cancer metastasis. Cancer Cell 27: 370-381, 2015.
46. Chen L, Fan X, Zhu J, Chen X, Liu Y and Zhou H: LncRNA MAGI2-AS3 inhibits the self-renewal of leukaemic stem cells by promoting TET2-dependent DNA demethylation of the LRIG1 promoter in acute myeloid leukaemia. RNA Biol 17: 784-793, 2020.
47. Nie Y, Zhou L, Wang H, Chen N, Jia L, Wang C, Wang Y, Chen J, Wen X, Niu C, *et al*: Profiling the epigenetic interplay of lncRNA RUNXOR and oncogenic RUNX1 in breast cancer cells by gene in situ cis-activation. Am J Cancer Res 9: 1635-1649, 2019.
48. Elsheikh SE, Green AR, Rakha EA, Powe DG, Ahmed RA, Collins HM, Soria D, Garibaldi JM, Paish CE, Ammar AA, *et al*: Global histone modifications in breast cancer correlate with tumor phenotypes, prognostic factors, and patient outcome. Cancer Res 69: 3802-3809, 2009.
49. Wang KC, Yang YW, Liu B, Sanyal A, Corces-Zimmerman R, Chen Y, Lajoie BR, Protacio A, Flynn RA, Gupta RA, *et al*: A long noncoding RNA maintains active chromatin to coordinate homeotic gene expression. Nature 472: 120-124, 2011.
50. Deng C, Li Y, Zhou L, Cho J, Patel B, Terada N, Li Y, Bungert J, Qiu Y, Huang S, *et al*: HoxBlinc RNA recruits Set1/MLL complexes to activate hox gene expression patterns and mesoderm lineage development. Cell Rep 14: 103-114, 2016.
51. Nagano T, Mitchell JA, Sanz LA, Pauler FM, Ferguson-Smith AC, Feil R and Fraser P: The Air noncoding RNA epigenetically silences transcription by targeting G9a to chromatin. Science 322: 1717-1720, 2008.
52. Xiu B, Chi Y, Liu L, Chi W, Zhang Q, Chen J, Guo R, Si J, Li L, Xue J, *et al*: LINC02273 drives breast cancer metastasis by epigenetically increasing AGR2 transcription. Mol Cancer 18: 187, 2019.
53. Hu A, Hong F, Li D, Jin Y, Kon L, Xu Z, He H and Xie Q: Long non-coding RNA ROR recruits histone transmethylase MLL1 to up-regulate TIMP3 expression and promote breast cancer progression. J Transl Med 19: 95, 2021.
54. Lai IL, Yang CA, Lin PC, Chan WL, Lee YT, Yen JC, Chang YS and Chang JG: Long noncoding RNA MIAT promotes non-small cell lung cancer proliferation and metastasis through MMP9 activation. Oncotarget 8: 98148-98162, 2017.
55. Wang WT, Chen TQ, Zeng ZC, Pan Q, Huang W, Han C, Fang K, Sun LY, Yang QQ, Wang D, *et al*: The lncRNA LAMP5-AS1 drives leukemia cell stemness by directly modulating DOT1L methyltransferase activity in MLL leukemia. J Hematol Oncol 13: 78, 2020.
56. Chu W, Zhang X, Qi L, Fu Y, Wang P, Zhao W, Du J, Zhang J, Zhan J, Wang Y, *et al*: The EZH2-PHACTR2-AS1-Ribosome axis induces genomic instability and promotes growth and metastasis in breast cancer. Cancer Res 80: 2737-2750, 2020.
57. Wanowska E, Samorowska K and Szczesniak MW: Emerging roles of long Noncoding RNAs in breast cancer epigenetics and epitranscriptomics. Front Cell Dev Biol 10: 922351, 2022.
58. Pandey RR, Mondal T, Mohammad F, Enroth S, Redrup L, Komorowski J, Nagano T, Mancini-Dinardo D and Kanduri C: Antisense Noncoding RNA mediates lineage-specific transcriptional silencing through Chromatin-Level regulation. Mol Cell 32: 232-246, 2008.
59. Gupta RA, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, Tsai MC, Hung T, Argani P, Rinn JL, *et al*: Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature 464: 1071-1076, 2010.
60. Kim K, Jutooru I, Chadalapaka G, Johnson G, Frank J, Burghardt R, Kim S and Safe S: HOTAIR is a negative prognostic factor and exhibits pro-oncogenic activity in pancreatic cancer. Oncogene 32: 1616-1625, 2013.
61. Niinuma T, Suzuki H, Nojima M, Nosho K, Yamamoto H, Takamaru H, Yamamoto E, Maruyama R, Nobuoka T, Miyazaki Y, *et al*: Upregulation of miR-196a and HOTAIR drive malignant character in gastrointestinal stromal tumors. Cancer Res 72: 1126-1136, 2012.
62. Kondo Y, Shinjo K and Katsushima K: Long non-coding RNAs as an epigenetic regulator in human cancers. Cancer Sci 108: 1927-1933, 2017.
63. Tsai MC, Manor O, Wan Y, Mosammaparast N, Wang JK, Lan F, Shi Y, Segal E and Chang HY: Long Noncoding RNA as modular scaffold of histone modification complexes. Science 329: 689-693, 2010.
64. Kumar S, Gonzalez EA, Rameshwar P and Etchegaray JP: Non-Coding RNAs as mediators of epigenetic changes in malignancies. Cancers (Basel) 12: 3657, 2020.
65. Liu Z, Sun M, Lu K, Liu J, Zhang M, Wu W, De W, Wang Z and Wang R: The long noncoding RNA HOTAIR contributes to cisplatin resistance of human lung adenocarcinoma cells via downregualtion of p21(WAF1/CIP1) expression. PLoS One 8: e77293, 2013.
66. Rinn JL, Kertesz M, Wang JK, Squazzo SL, Xu X, Brugmann SA, Goodnough LH, Helms JA, Farnham PJ, Segal E and Chang HY: Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. Cell 129: 1311-1323, 2007.
67. Liu YW, Xia R, Lu K, Xie M, Yang F, Sun M, De W, Wang C and Ji G: LincRNAFEZF1-AS1 represses p21 expression to promote gastric cancer proliferation through LSD1-Mediated H3K4me2 demethylation. Mol Cancer 16: 39, 2017.
68. Pang B, Wang Q, Ning S, Wu J, Zhang X, Chen Y and Xu S: Landscape of tumor suppressor long noncoding RNAs in breast cancer. J Exp Clin Cancer Res 38: 79, 2019.
69. Huo Y, Li Q, Wang X, Jiao X, Zheng J, Li Z and Pan X: MALAT1 predicts poor survival in osteosarcoma patients and promotes cell metastasis through associating with EZH2. Oncotarget 8: 46993-47006, 2017.
70. Amodio N, Raimondi L, Juli G, Stamato MA, Caracciolo D, Tagliaferri P and Tassone P: MALAT1: A druggable long non-coding RNA for targeted anti-cancer approaches. J Hematol Oncol 11: 63, 2018.
71. Chi JS, Li JZ, Jia JJ, Zhang T, Liu XM and Yi L: Long non-coding RNA ANRIL in gene regulation and its duality in atherosclerosis. J Huazhong Univ Sci Technolog Med Sci 37: 816-822, 2017.
72. Meseure D, Vacher S, Alsibai KD, Nicolas A, Chemlali W, Caly M, Lidereau R, Pasmant E, Callens C and Bieche I: Expression of ANRIL-Polycomb Complexes-CDKN2A/B/ARF genes in breast tumors: Identification of a Two-Gene (EZH2/CBX7) signature with independent prognostic value. Mol Cancer Res 14: 623-633, 2016.
73. Puvvula PK, Desetty RD, Pineau P, Marchio A, Moon A, Dejean A and Bischof O: Long noncoding RNA PANDA and scaffold-attachment-factor SAFA control senescence entry and exit. Nat Commun 5: 5323, 2014.

74. Portoso M, Ragazzini R, Brenčič Ž, Moiani A, Michaud A, Vassilev I, Wassef M, Servant N, Sargueil B and Margueron R: PRC2 is dispensable for HOTAIR-mediated transcriptional repression. EMBO J 36: 981-994, 2017.
75. Wang X, Arai S, Song X, Reichart D, Du K, Pascual G, Tempst P, Rosenfeld MG, Glass CK and Kurokawa R: Induced ncRNAs allosterically modify RNA-binding proteins in cis to inhibit transcription. Nature 454: 126-130, 2008.
76. Wang XH and Li J: CircAGFG1 aggravates the progression of cervical cancer by downregulating p53. Eur Rev Med Pharmacol Sci 24: 1704-1711, 2020.
77. Zhang G, Chen X, Ma L, Ding R, Zhao L, Ma F and Deng X: LINC01419 facilitates hepatocellular carcinoma growth and metastasis through targeting EZH2-regulated RECK. Aging (Albany NY) 12: 11071-11084, 2020.
78. Chen XJ and An N: Long noncoding RNA ATB promotes ovarian cancer tumorigenesis by mediating histone H3 lysine 27 trimethylation through binding to EZH2. J Cell Mol Med 25: 37-46, 2021.
79. Wu L, Gong Y, Yan T and Zhang H: LINP1 promotes the progression of cervical cancer by scaffolding EZH2, LSD1, and DNMT1 to inhibit the expression of KLF2 and PRSS8. Biochem Cell Biol 98: 591-599, 2020.
80. Zhang J, Li WY, Yang Y, Yan LZ, Zhang SY, He J and Wang JX: LncRNA XIST facilitates cell growth, migration and invasion via modulating H3 histone methylation of DKK1 in neuroblastoma. Cell Cycle 18: 1882-1892, 2019.
81. Li Z, Yu D, Li H, Lv Y and Li S: Long non-coding RNA UCA1 confers tamoxifen resistance in breast cancer endocrinotherapy through regulation of the EZH2/p21 axis and the PI3K/AKT signaling pathway. Int J Oncol 54: 1033-1042, 2019.
82. Dong H, Wang W, Mo S, Chen R, Zou K, Han J, Zhang F and Hu J: SP1-induced lncRNA AGAP2-AS1 expression promotes chemoresistance of breast cancer by epigenetic regulation of MyD88. J Exp Clin Cancer Res 37: 202, 2018.
83. Loe AKH, Zhu L and Kim TH: Chromatin and noncoding RNA-mediated mechanisms of gastric tumorigenesis. Exp Mol Med 55: 22-31, 2023.
84. Qiu Y, Xu M and Huang S: Long noncoding RNAs: Emerging regulators of normal and malignant hematopoiesis. Blood 138: 2327-2336, 2021.
85. Qiu Y and Huang S: CTCF-mediated genome organization and leukemogenesis. Leukemia 34: 2295-2304, 2020.
86. Ribeiro-Silva C, Vermeulen W and Lans H: SWI/SNF: Complex complexes in genome stability and cancer. DNA Repair (Amst) 77: 87-95, 2019.
87. Bammidi LS and Gayen S: Multifaceted role of CTCF in X-chromosome inactivation. Chromosoma 133: 217-231, 2024.
88. Martitz A and Schulz EG: Spatial orchestration of the genome: Topological reorganisation during X-chromosome inactivation. Curr Opin Genet Dev 86: 102198, 2024.
89. Engreitz JM, Pandya-Jones A, McDonel P, Shishkin A, Sirokman K, Surka C, Kadri S, Xing J, Goren A, Lander ES, *et al*: The Xist lncRNA exploits three-dimensional genome architecture to spread across the X chromosome. Science 341: 1237973, 2013.
90. Kung JT, Kesner B, An JY, Ahn JY, Cifuentes-Rojas C, Colognori D, Jeon Y, Szanto A, del Rosario BC, Pinter SF, *et al*: Locus-specific targeting to the X chromosome revealed by the RNA interactome of CTCF. Mol Cell 57: 361-375, 2015.
91. Luo H, Zhu G, Eshelman MA, Fung TK, Lai Q, Wang F, Zeisig BB, Lesperance J, Ma X, Chen S, *et al*: HOTTIP-dependent R-loop formation regulates CTCF boundary activity and TAD integrity in leukemia. Mol Cell 82: 833-851 e811, 2022.
92. Zhu G, Luo H, Feng Y, Guryanova OA, Xu J, Chen S, Lai Q, Sharma A, Xu B, Zhao Z, *et al*: HOXBLINC long non-coding RNA activation promotes leukemogenesis in NPM1-mutant acute myeloid leukemia. Nat Commun 12: 1956, 2021.
93. Lai Q, Hamamoto K, Luo H, Zaroogian Z, Zhou C, Lesperance J, Zha J, Qiu Y, Guryanova OA, Huang S and Xu B: NPM1 mutation reprograms leukemic transcription network via reshaping TAD topology. Leukemia 37: 1732-1736, 2023.
94. Venkatraman A, He XC, Thorvaldsen JL, Sugimura R, Perry JM, Tao F, Zhao M, Christenson MK, Sanchez R, Yu JY, *et al*: Maternal imprinting at the H19-Igf2 locus maintains adult haematopoietic stem cell quiescence. Nature 500: 345-349, 2013.
95. Hacisuleyman E, Goff LA, Trapnell C, Williams A, Henao-Mejia J, Sun L, McClanahan P, Hendrickson DG, Sauvageau M, Kelley DR, *et al*: Topological organization of multichromosomal regions by the long intergenic noncoding RNA Firre. Nat Struct Mol Biol 21: 198-206, 2014.
96. Hanly DJ, Esteller M and Berdasco M: Interplay between long non-coding RNAs and epigenetic machinery: Emerging targets in cancer? Philos Trans R Soc Lond B Biol Sci 373, 2018.
97. Reddy D, Bhattacharya S, Levy M, Zhang Y, Gogol M, Li H, Florens L and Workman JL: Paraspeckles interact with SWI/SNF subunit ARID1B to regulate transcription and splicing. EMBO Rep 24: e55345, 2023.
98. Bhattacharya A, Wang K, Penailillo J, Chan CN, Fushimi A, Yamashita N, Daimon T, Haratake N, Ozawa H, Nakashoji A, *et al*: MUC1-C regulates NEAT1 lncRNA expression and paraspeckle formation in cancer progression. Oncogene 43: 2199-2214, 2024.
99. Lee VH, Tsang RK, Lo AWI, Chan SY, Chung JC, Tong CC, Leung TW and Kwong DL: SMARCB1 (INI-1)-Deficient sinonasal carcinoma: A systematic review and pooled analysis of treatment outcomes. Cancers (Basel) 14: 3285, 2022.
100. Wang X, Gong Y, Jin B, Wu C, Yang J, Wang L, Zhang Z and Mao Z: Long non-coding RNA urothelial carcinoma associated 1 induces cell replication by inhibiting BRG1 in 5637 cells. Oncol Rep 32: 1281-1290, 2014.
101. Huang M, Wang H, Hu X and Cao X: lncRNA MALAT1 binds chromatin remodeling subunit BRG1 to epigenetically promote inflammation-related hepatocellular carcinoma progression. Oncoimmunology 8: e1518628, 2019.
102. Lino Cardenas CL, Kessinger CW, Cheng Y, MacDonald C, MacGillivray T, Ghoshhajra B, Huleihel L, Nuri S, Yeri AS, Jaffer FA, *et al*: An HDAC9-MALAT1-BRG1 complex mediates smooth muscle dysfunction in thoracic aortic aneurysm. Nat Commun 9: 1009, 2018.
103. Neve B, Jonckheere N, Vincent A and Van Seuningen I: Epigenetic regulation by lncRNAs: An overview focused on UCA1 in colorectal cancer. Cancers (Basel) 10: 1009, 2018.
104. Chiba H, Muramatsu M, Nomoto A and Kato H: Two human homologues of Saccharomyces cerevisiae SWI2/SNF2 and Drosophila brahma are transcriptional coactivators cooperating with the estrogen receptor and the retinoic acid receptor. Nucleic Acids Res 22: 1815-1820, 1994.
105. Wang Y, He L, Du Y, Zhu P, Huang G, Luo J, Yan X, Ye B, Li C, Xia P, *et al*: The long noncoding RNA lncTCF7 promotes self-renewal of human liver cancer stem cells through activation of Wnt signaling. Cell Stem Cell 16: 413-425, 2015.
106. Li Y, Li W, Hoffman AR, Cui J and Hu JF: The Nucleus/Mitochondria-Shuttling LncRNAs function as new epigenetic regulators of mitophagy in cancer. Front Cell Dev Biol 9: 699621, 2021.
107. Prensner JR, Iyer MK, Sahu A, Asangani IA, Cao Q, Patel L, Vergara IA, Davicioni E, Erho N, Ghadessi M, *et al*: The long noncoding RNA SChLAP1 promotes aggressive prostate cancer and antagonizes the SWI/SNF complex. Nat Genet 45: 1392-1398, 2013.
108. Cimadamore A, Gasparrini S, Mazzucchelli R, Doria A, Cheng L, Lopez-Beltran A, Santoni M, Scarpelli M and Montironi R: Long Non-coding RNAs in prostate cancer with emphasis on second chromosome locus associated with Prostate-1 expression. Front Oncol 7: 305, 2017.
109. Boo SH and Kim YK: The emerging role of RNA modifications in the regulation of mRNA stability. Exp Mol Med 52: 400-408, 2020.
110. de Santiago PR, Blanco A, Morales F, Marcelain K, Harismendy O, Sjöberg Herrera M and Armisén R: Immune-related lncRNA LINC00944 responds to variations in ADAR1 levels and it is associated with breast cancer prognosis. Life Sci 268: 118956, 2021.
111. Sun Y, Ge J, Shao F, Ren Z, Huang Z, Ding Z, Dong L, Chen J, Zhang J and Zang Y: Long noncoding RNA AI662270 promotes kidney fibrosis through enhancing METTL3-mediated m^6A modification of CTGF mRNA. FASEB J 37: e23071, 2023.
112. Cao Y, Di X, Cong S, Tian C, Wang Y, Jin X, Zhao M, Zhou X, Li R and Wang K: RBM10 recruits METTL3 to induce N6-methyladenosine-MALAT1-dependent modification, inhibiting the invasion and migration of NSCLC. Life Sci 315: 121359, 2023.
113. Fang Y, Wu X, Gu Y, Shi R, Yu T, Pan Y, Zhang J, Jing X, Ma P and Shu Y: LINC00659 cooperated with ALKBH5 to accelerate gastric cancer progression by stabilising JAK1 mRNA in an m^6 A-YTHDF2-dependent manner. Clin Transl Med 13: e1205, 2023.
114. Salameh A, Lee AK, Cardo-Vila M, Nunes DN, Efstathiou E, Staquicini FI, Dobroff AS, Marchiò S, Navone NM, Hosoya H, *et al*: PRUNE2 is a human prostate cancer suppressor regulated by the intronic long noncoding RNA PCA3. Proc Natl Acad Sci USA 112: 8403-8408, 2015.

115. Zhu L, Zhu Y, Han S, Chen M, Song P, Dai D, Xu W, Jiang T, Feng L, Shin VY, *et al*: Impaired autophagic degradation of lncRNA ARHGAP5-AS1 promotes chemoresistance in gastric cancer. Cell Death Dis 10: 383, 2019.
116. Mao J, Qiu H and Guo L: LncRNA HCG11 mediated by METTL14 inhibits the growth of lung adenocarcinoma via IGF2BP2/LATS1. Biochem Biophys Res Commun 580: 74-80, 2021.
117. Picardi E, D'Erchia AM, Gallo A, Montalvo A and Pesole G: Uncovering RNA editing sites in long Non-Coding RNAs. Front Bioeng Biotechnol 2: 64, 2014.
118. Ma CP, Liu H, Yi-Feng Chang I, Wang WC, Chen YT, Wu SM, Chen HW, Kuo YP, Shih CT, Li CY and Tan BC: ADAR1 promotes robust hypoxia signaling via distinct regulation of multiple HIF-1alpha-inhibiting factors. EMBO Rep 20: e47107, 2019.
119. Salameh A, Lee AK, Cardó-Vila M, Nunes DN, Efstathiou E, Staquicini FI, Dobroff AS, Marchiò S, Navone NM, Hosoya H, *et al*: PRUNE2 is a human prostate cancer suppressor regulated by the intronic long noncoding RNA. Proc Natl Acad Sci USA 112: 8403-8408, 2015.
120. Arun G, Diermeier S, Akerman M, Chang KC, Wilkinson JE, Hearn S, Kim Y, MacLeod AR, Krainer AR and Norton L: Differentiation of mammary tumors and reduction in metastasis upon Malat1 lncRNA loss. Genes Dev 30: 34-51, 2016.
121. Zhao C, Ling X, Xia Y, Yan B and Guan Q: The m6A methyltransferase METTL3 controls epithelial-mesenchymal transition, migration and invasion of breast cancer through the MALAT1/miR-26b/HMGA2 axis. Cancer Cell Int 21: 441, 2021.
122. Sun T, Wu Z, Wang X, Wang Y, Hu X, Qin W, Lu S, Xu D, Wu Y, Chen Q, *et al* LNC942 promoting METTL14-mediated m6A methylation in breast cancer cell proliferation and progression. Oncogene 39: 5358-5372, 2020.
123. Pu J, Xu Z, Huang Y, Nian J, Yang M, Fang Q, Wei Q, Huang Z, Liu G, Wang J, *et al*: N^6-methyladenosine-modified FAM111A-DT promotes hepatocellular carcinoma growth via epigenetically activating FAM111A. Cancer Sci 114: 3649-3665, 2023.
124. Zhou L, Jiang J, Huang Z, Jin P, Peng L, Luo M, Zhang Z, Chen Y, Xie N, Gao W, *et al*: Hypoxia-induced lncRNA STEAP3-AS1 activates Wnt/β-catenin signaling to promote colorectal cancer progression by preventing m6A-mediated degradation of STEAP3 mRNA. Mol Cancer 21: 168, 2022.
125. Wang X, Liu C, Zhang S, Yan H, Zhang L, Jiang A, Liu Y, Feng Y, Li D, Guo Y, *et al*: N^6-methyladenosine modification of MALAT1 promotes metastasis via reshaping nuclear speckles. Dev Cell 56: 702-715.e8, 2021.
126. Yang H, Hu Y, Weng M, Liu X, Wan P, Hu Y, Ma M, Zhang Y, Xia H and Lv K: Hypoxia inducible lncRNA-CBSLR modulates ferroptosis through m6A-YTHDF2-dependent modulation of CBS in gastric cancer. J Adv Res 37: 91-106, 2022.
127. Wang S, Wang Y, Zhang Z, Zhu C, Wang C, Yu F and Zhao E: Long Non-Coding RNA NRON promotes tumor proliferation by regulating ALKBH5 and nanog in gastric cancer. J Cancer 12: 6861-6872, 2021.
128. Zhang S, Zhao BS, Zhou A, Lin K, Zheng S, Lu Z, Chen Y, Sulman EP, Xie K, Bögler O, *et al*: m^6A Demethylase ALKBH5 maintains tumorigenicity of glioblastoma Stem-like cells by sustaining FOXM1 expression and cell proliferation program. Cancer Cell 31: 591-606.e6, 2017.
129. Zou Z, Zhou S, Liang G, Tang Z, Li K, Tan S, Zhang X and Zhu X: The pan-cancer analysis of the two types of uterine cancer uncovered clinical and prognostic associations with m6A RNA methylation regulators. Mol Omics 17: 438-453, 2021.
130. Zhu P, He F, Hou Y, Tu G, Li Q, Jin T, Zeng H, Qin Y, Wan X, Qiao Y *et al*: A novel hypoxic long noncoding RNA KB-1980E6.3 maintains breast cancer stem cell stemness via interacting with IGF2BP1 to facilitate c-Myc mRNA stability. Oncogene 40: 1609-1627, 2021.
131. Nadhan R, Isidoro C, Song YS and Dhanasekaran DN: LncRNAs and the cancer epigenome: Mechanisms and therapeutic potential. Cancer Lett 605: 217297, 2024.
132. Yang L, Tang L, Min Q, Tian H, Li L, Zhao Y, Wu X, Li M, Du F, Chen Y, *et al*: Emerging role of RNA modification and long noncoding RNA interaction in cancer. Cancer Gene Ther 31: 816-830, 2024.
133. Kim SY, Na MJ, Yoon S, Shin E, Ha JW, Jeon S and Nam SW: The roles and mechanisms of coding and noncoding RNA variations in cancer. Exp Mol Med 56: 1909-1920, 2024.
134. Quinn JJ and Chang HY: Unique features of long non-coding RNA biogenesis and function. Nat Rev Genet 17: 47-62, 2016.
135. Liu S, Jiao B, Zhao H, Liang X, Jin F, Liu X and Hu JF: LncRNAs-circRNAs as rising epigenetic binary superstars in regulating lipid metabolic reprogramming of cancers. Adv Sci (Weinh) 11: e2303570, 2024.
136. Mattick JS, Amaral PP, Carninci P, Carpenter S, Chang HY, Chen LL, Chen R, Dean C, Dinger ME, Fitzgerald KA, *et al*: Long non-coding RNAs: Definitions, functions, challenges and recommendations. Nat Rev Mol Cell Biol 24: 430-447, 2023.
137. Liu SJ, Dang HX, Lim DA, Feng FY and Maher CA: Long noncoding RNAs in cancer metastasis. Nat Rev Cancer 21: 446-460, 2021.
138. Qian Y, Shi L and Luo Z: Long Non-coding RNAs in Cancer: Implications for diagnosis, prognosis, and therapy. Front Med (Lausanne) 7: 612393, 2020.
139. Gong C, Li Z, Ramanujan K, Clay I, Zhang Y, Lemire-Brachat S and Glass DJ: A long non-coding RNA, LncMyoD, regulates skeletal muscle differentiation by blocking IMP2-mediated mRNA translation. Dev Cell 34: 181-191, 2015.
140. Davodabadi F, Farasati Far B, Sargazi S, Fatemeh Sajjadi S, Fathi-Karkan S, Mirinejad S, Ghotekar S, Sargazi S and Rahman MM: Nanomaterials-based targeting of long Non-Coding RNAs in cancer: A Cutting-edge review of current trends. ChemMedChem 19: e202300528, 2024.
141. Han S, Cao Y, Guo T, Lin Q and Luo F: Targeting lncRNA/Wnt axis by flavonoids: A promising therapeutic approach for colorectal cancer. Phytother Res 36: 4024-4040, 2022.
142. Parashar D, Singh A, Gupta S, Sharma A, Sharma MK, Roy KK, Chauhan SC and Kashyap VK: Emerging roles and potential applications of Non-Coding RNAs in Cervical cancer. Genes (Basel) 13: 1254, 2022.
143. Goyal A, Myacheva K, Gross M, Klingenberg M, Duran Arque B and Diederichs S: Challenges of CRISPR/Cas9 applications for long non-coding RNA genes. Nucleic Acids Res 45: e12, 2017.
144. Cetinkaya M and Baran Y: MicroRNAs and long non-coding RNAs as novel targets in Anti-cancer drug development. Curr Pharm Biotechnol 24: 913-925, 2023.
145. Ozcan G, Ozpolat B, Coleman RL, Sood AK and Lopez-Berestein G: Preclinical and clinical development of siRNA-based therapeutics. Adv Drug Deliv Rev 87: 108-119, 2015.
146. Wahlestedt C: Targeting long non-coding RNA to therapeutically upregulate gene expression. Nat Rev Drug Discov 12: 433-446, 2013.
147. Alegra-Torres JA, Baccarelli A and Bollati V: Epigenetics and lifestyle. Epigenomics 3: 267-277, 2011.
148. Basu AK: DNA Damage, mutagenesis and cancer. Int J Mol Sci 19: 970, 2018.
149. Cheng D, Deng J, Zhang B, He X, Meng Z, Li G, Ye H, Zheng S, Wei L, Deng X, *et al*: LncRNA HOTAIR epigenetically suppresses miR-122 expression in hepatocellular carcinoma via DNA methylation. EBioMedicine 36: 159-170, 2018.
150. Vaasjo LO: LncRNAs and chromatin modifications pattern m6A methylation at the untranslated regions of mRNAs. Front Genet 13: 866772, 2022.
151. Vaid R, Thombare K, Mendez A, Burgos-Panadero R, Djos A, Jachimowicz D, Lundberg KI, Bartenhagen C, Kumar N, Tümmler C, *et al*: METTL3 drives telomere targeting of TERRA lncRNA through m6A-dependent R-loop formation: A therapeutic target for ALT-positive neuroblastoma. Nucleic Acids Res 52: 2648-2671, 2024.
152. Anastasiadou E, Jacob LS and Slack FJ: Non-coding RNA networks in cancer. Nat Rev Cancer 18: 5-18, 2018.
153. Marchese FP, Raimondi I and Huarte M: The multidimensional mechanisms of long noncoding RNA function. Genome Biol 18: 206, 2017.
154. Cho SW, Xu J, Sun R, Mumbach MR, Carter AC, Chen YG, Yost KE, Kim J, He J, Nevins SA, *et al*: Promoter of lncRNA Gene PVT1 is a Tumor-suppressor DNA boundary element. Cell 173: 1398-1412.e22, 2018.
155. Arun G, Aggarwal D and Spector DL: MALAT1 Long Non-coding RNA: Functional implications. Noncoding RNA 6: 22, 2020.
156. Chen PB, Chen HV, Acharya D, Rando OJ and Fazzio TG: R loops regulate promoter-proximal chromatin architecture and cellular differentiation. Nat Struct Mol Biol 22: 999-1007, 2015.

157. Chu C, Qu K, Zhong FL, Artandi SE and Chang HY: Genomic maps of long Noncoding RNA occupancy reveal principles of RNA-Chromatin interactions. Mol Cell 44: 667-678, 2011.
158. Chu C and Chang HY: ChIRP-MS: RNA-directed proteomic discovery. Methods Mol Biol 1861: 37-45, 2018.
159. de Lera AR and Ganesan A: Epigenetic polypharmacology: From combination therapy to multitargeted drugs. Clin Epigenetics 8: 105, 2016.
160. Delgado-Morales R, Agís-Balboa RC, Esteller M and Berdasco M: Epigenetic mechanisms during ageing and neurogenesis as novel therapeutic avenues in human brain disorders. Clin Epigenetics 9, 2017.
161. Wu SC, Kallin EM and Zhang Y: Role of H3K27 methylation in the regulation of lncRNA expression. Cell Res 20: 1109-1116, 2010.
162. Kornienko AE, Dotter CP, Guenzl PM, Gisslinger H, Gisslinger B, Cleary C, Kralovics R, Pauler FM and Barlow DP: Long non-coding RNAs display higher natural expression variation than protein-coding genes in healthy humans. Genome Biol 17: 14, 2016.
163. Pang KC, Frith MC and Mattick JS: Rapid evolution of noncoding RNAs: Lack of conservation does not mean lack of function. Trends Genet 22: 1-5, 2006.
164. Bohmdorfer G and Wierzbicki AT: Control of chromatin structure by long noncoding RNA. Trends Cell Biol 25: 623-632, 2015.
165. Xing Z, Lin A, Li C, Liang K, Wang S, Liu Y, Park PK, Qin L, Wei Y, Hawke DH, *et al*: lncRNA directs cooperative epigenetic regulation downstream of chemokine signals. Cell 159: 1110-1125, 2014.