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REVIEW

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Mutual interaction of lncRNAs and epigenetics: focusing on cancer

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Abstract

Long noncoding RNAs are characterized as noncoding transcripts longer than 200 nucleotides in response to a variety of functions within the cells. They are involved in almost all cellular mechanisms so as epigenetics. Given that epigenetics is an important phenomenon, which participates in the biology of complex diseases, many valuable studies have been performed to demonstrate the control status of lncRNAs and epigenetics. DNA methylation and histone modifications as epigenetic mechanisms can regulate the expression of lncRNAs by affecting their coding genes. Reciprocally, the three-dimensional structure of lncRNAs could mechanistically control the activity of epigenetic-related enzymes. Dysregulation in the mutual interaction between epigenetics and lncRNAs is one of the hallmarks of cancer. These mechanisms are either directly or indirectly involved in various cancer properties such as proliferation, apoptosis, invasion, and metastasis. For instance, lncRNA HOTAIR plays a role in regulating the expression of many genes by interacting with epigenetic factors such as DNA methyltransferases and EZH2, and thus plays a role in the initiation and progression of various cancers. Conversely, the expression of this lncRNA is also controlled by epigenetic factors. Therefore, focusing on this reciprocated interaction can apply to cancer management and the identification of prognostic, diagnostic, and druggable targets. In the current review, we discuss the reciprocal relationship between lncRNAs and epigenetic mechanisms to promote or prevent cancer progression and find new potent biomarkers and targets for cancer diagnosis and therapy.

Keywords lncRNA, DNA methylation, Histone methylation, Histone acetylation, Histone deacetylation, Cancers, N6-methyl-adenosine, m6A

Introduction

Noncoding RNAs comprise over ninety-five percent of human transcriptome [1], which are categorized into two classes based on their length, including small noncoding RNAs (including microRNAs, small interfering RNAs, and snoRNAs) and long noncoding RNAs (lncRNA) [2]. LncRNAs are the major class of noncoding RNAs whose length varies from 200 bp to 10 kb [3–5]. They mostly do not have any open reading frame to be translated into proteins; thus, lncRNAs have no protein-coding potential or rarely code for less than 100 amino acids [5, 6]. According to the alignment of lncRNAs with protein-coding genes, they contain introns and exons. Most of them have capping, splicing, and polyadenylation like protein-coding genes and RNAs. They are transcribed

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by RNA polymerase II [7] and poorly conserved with low expression levels and high tissue specificity [8–10]. For years, lncRNAs were known as un-functional products; however, nowadays we know them as having a wide spectrum of functions inside the cell. LncRNAs play various roles in many cellular mechanisms, such as gene expression, chromatin dynamics, apoptosis, and parental imprinting [11–13]. In addition, many lncRNAs can interact with microRNAs (miRs) like a sponge or compete for endogenous RNA (ceRNA) [14]. They are associated with different epigenetic phenomena and take part in two major epigenetic processes, including histone modification, through networking-related proteins such as protein members of the polycomb repressive complex (PRC2), and DNA methylation through direct and indirect cooperation with methylation-related enzymes [7, 15]. Accordingly, dysregulation in the expression of lncRNAs or their functions could affect the pathogenesis of diseases such as cancers. This could be conducted by different mechanisms, e.g., interaction with proteins or regulation of the expression of cancer-related genes [16]. Our study aims to summarize a review of how the reciprocal relationship between lncRNA and epigenetic mechanisms can promote or prevent cancer progression, and whether this field can provide new potent biomarkers and targets for cancer diagnosis and therapy.

The association of epigenetics and lncRNAs

As fundamental epigenetic mechanisms such as DNA methylation and histone modifications can normally affect the expression of the protein-coding genes, they can also regulate the expression of noncoding RNAs (i.e., Figs. 1A and 2A). In this regard, some lncRNAs reciprocally can affect DNA methylation enzymes, including DNA methyltransferases (DNMTs), the ten-eleven translocation (TET), methyl-CpG-binding domains (MBDs), and histone modification enzymes. Altogether, aberrant DNA methylation and histone modification of lncRNA-coding genes or abnormal activity of DNA methylation/histone modification enzymes mediated by lncRNAs can lead to various cancers [17–21].

The effect of lncRNA on different cancers

Breast cancer

Breast cancer (BC) is the leading cause of cancer deaths in women and exhibits high heterogeneity and complexity, which elevates the importance of finding novel markers for this cancer. Numerous studies have been performed on the role of lncRNAs in this cancer. For example, lncRNA MEG3 is encoded by maternally expressed gene 3, an imprinted gene that acts as a tumor suppressor gene and is dysregulated in different kinds of cancers. MEG3 regulates proliferation, migration, and invasion by inhibiting the p53 tumoral pathway. miR-506 regulates the expression of DNMT1 via SP1 and SP3 transcription factors and reduces MEG3 promoter methylation, and consequently, an increased amount of MEG3 regulates the migration and invasion of BC cells. Therefore, the downregulation of miR-506 causes hypermethylation in the MEG3 promoter and induces more proliferation, migration, and invasion in BC cells by interacting with p53 [22]. LINC00472 is another tumor suppressor regulated by promoter methylation, which is associated with better disease outcomes [1]. Additionally, Basal-like breast cancer Associated Transcript-1 (BLAT1) lncRNA is significantly upregulated in Basal-like breast cancer

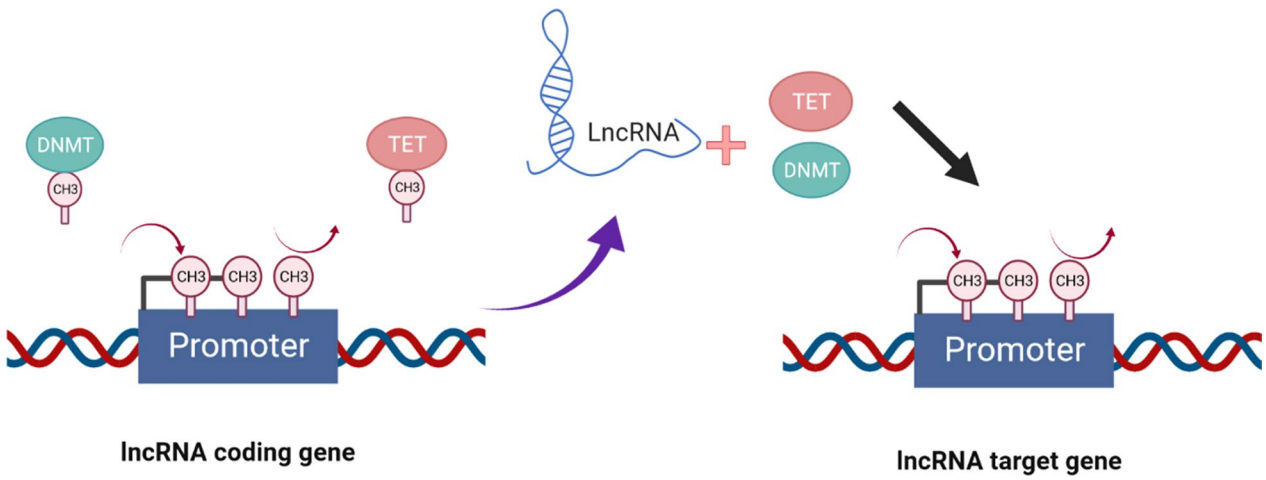

Fig. 1 Reciprocal interaction between lncRNAs and DNA promoter methylation. **A** The expression level of lncRNAs is controlled by DNA methylation and DNA-methylating enzymes in the promoter region of their codding genes. **B** Inversely, some lncRNAs can control the expression of various genes by interacting with DNA-methylating enzymes with different mechanisms

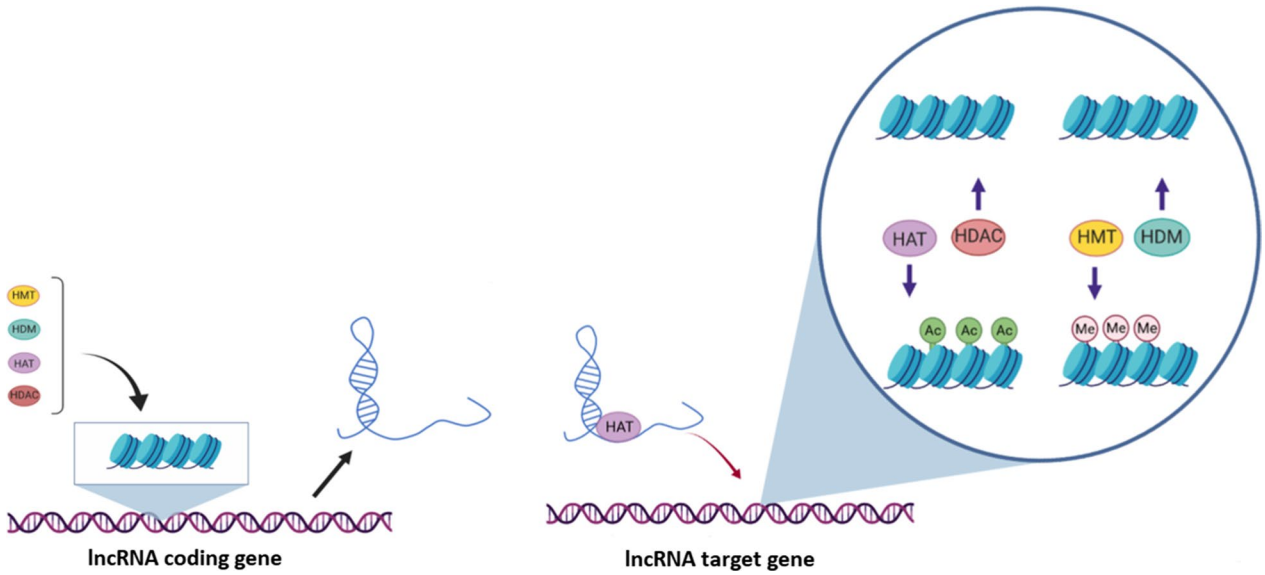

Fig. 2 Interaction between lncRNA and histone modifications. **A** The expression level of lncRNAs can be regulated by histone modification mechanisms. **B** lncRNAs can affect histone modification mechanisms, including histone acetylation and histone methylation

(BLBC) cells and this upregulation promotes the aggressive phenotype of BLBC by interfering with cell survival pathway and suppressing apoptosis [23].

Colorectal cancer

Colorectal cancer (CRC) is one of the deadliest and most highly heterogenic cancers with an increasing incidence among young adults every year [24–26]. CRC shows the global DNA hypomethylation of the genome and methylation in the promoter regions. According to studies on this issue, LINC00460 is overexpressed in CRC due to promoter CpGs hypomethylation. This lncRNA can be a valuable therapeutic target because it helps tumor metastasis by promoting invasion and migration [27]. LINC00460 plays an important role in CRC progression and drug resistance. This role is played through different mechanisms such as interacting with miRs such as sponging miR-939-5p or inhibition of MiR-613 [28–30]. PVT1, involved in EMT and angiogenesis, urothelial carcinoma-associated 1 (UCA1), and TRPM2-AS are upregulated lncRNAs in colorectal adenocarcinoma that are affected by promoter hypomethylation [31]. On the other hand, LINC00472, which is likely to be involved in cancer-related mechanisms such as cell cycle, cell migration, cell growth, and DNA repair, is downregulated in CRCs by promoter hypermethylation. Studies revealed that according to the low expression of lncRNAs, the LINC00472 promoter methylation state was a more reliable biomarker for CRC diagnosis than its expression level [32]. ZNF582-AS1 is another hypermethylated and downregulated lncRNA during CRC. This lncRNA is negatively involved in colony formation. In addition, it is hypothetically involved in G-protein coupled receptor signaling pathway [5]. Interestingly, hypermethylation in the gene body activates GATA2-AS1, which seems to correlate with poor survival in CRC [31].

Gastric cancer

Another common type of cancer with a low survival rate is GC [33], which shows a great change in epigenetic and methylation state. Previously described tumor suppressor MEG3 is significantly downregulated in GC due to hypermethylation as well. MEG3 takes part in ATP4B regulation by targeting miR-181a-5p. It also affects the expression of miR-21 so MEG3 dysregulation causes cancer promotion by increasing proliferation and apoptosis [34]. KCNKI5-ASI is another tumor suppressor that targets miR-21 and affects the levels of BCL-2, Bax, and matrix metalloproteinase (MMP)-2 and -9 [35]. Similar to other cancer types mentioned above, Linc00472 has a central role in GC by sponging miR-196a, miR-93, miR-24-3p, and several other oncomirs and suppressing cell growth and motility [36]. In addition, Linc00086 is seen to be downregulated in GC. This downregulation might be due to promoter hypermethylation under the influence of methyl-CpG-binding protein 2 (MeCP2) [37].

Cervical cancer

Cervical cancer has the 4th place of the most common and deadliest cancers among women. The vast majority of cases are caused by human papillomavirus (HPV) infection. The progress from lesions caused by HPV to

cervical cancer is a long process; so early diagnosis is very important [38, 39]. LncRNA SOX21-AS1 is hypomethylated and upregulated in patients with cervical cancer. However, it acts as a tumor suppressor in many other cancers. This tumor heterogeneity gives a high prognostic value to SOX21-AS1. SOX21-AS1 is involved in sequence-specific DNA binding of RNA polymerase II transcription factor and SOX2 regulation [40]. Additionally, LINC00592 shows aberrant expression and CpG hypomethylation in cervical cancer. Its biological function has not been detected but it might have a role in transcription and cell integrity. LINC00592 also binds to two cancer-related miRs, miR-34a, and miR-449a [41]. GAS5, another methylation-effected lncRNA, is a potential biomarker and can inhibit cervical cancer. GAS5 inhibits proliferation, cell cycle progression, invasion, and migration; and additionally, induces apoptosis [42].

Pancreatic cancer

Pancreatic cancer (PC) is the 4th leading cause of cancer death worldwide. It is hard to diagnose PC in the early stages and this problem greatly reduces the chance of survival in patients. In PC cells, A2M-AS1 and DLEU2 hypomethylated in the promoter and overexpressed compared to a normal cell. MIR155HG, ITGB2-AS1, TSPOAP1-AS1, and LOC642852 are hypermethylated, but contrary to our expectation, ITGB2-AS1 shows more expression in cancer cells than healthy cells [43].

Lung cancer

Lung cancer is common cancer that has the poorest outcome among cancers [44]. NSCLC is the most common form of lung cancer with a high mortality rate. According to the studies on lncRNAs involved in NSCLC, LOC146880 positively correlates with the expression of KPNA2, a potential cancer-related gene. LOC146880 expression is associated with promoter methylation and its high expression is associated with poor overall survival in NSCLC patients [45]. In addition, AFAP1-AS1 is hypomethylated and upregulated and plays an oncogenic role in NSCLC. It can upregulate AFAP1 and promote cell migration [46].

Glioma

Glioma is the most common type of primary tumor in the brain and spinal cord that exhibits high mortality. Several lncRNAs are found to be dysregulated due to changes in promoter methylation state in glioma. Long noncoding RNA Homeobox transcript antisense intergenic RNA (HOTAIR) is one of the lncRNAs that have been studied in connection with various cancers (Table 1). HOTAIR is overexpressed in glioma and has prognostic values for both expression level and methylation state. HOTAIR expression is regulated by HOXA9 and it seems that part of HOTAIR function is mediating HOXA9 actions [47]. There are other oncogenic lncRNAs affected by hypomethylation, including H19, CYTOR, AGAAP2-AS1, MIR155HG, MIR4435-2HG, and LOC285758. The expression of these lncRNAs is associated with tumor grade and subtyping [48, 49]. Tumor suppressor MEG3 is also involved in glioma and, as mentioned above, exerts its effect through the p53 pathway [50].

Esophageal squamous cell cancer

Esophageal cancer squamous cell (ESCC) is the least studied cancer with a poor survival rate. ESCC accounts for 90% of esophageal cancer cases. Similar to other cancers described above, MEG3 plays a tumor-suppressive role in ESCC. MEG3 acts as a ceRNA for miR-9 and regulates E-cadherin and FOXO1 expression. Significant MEG3 downregulation caused by promoter hypermethylation leads to esophageal cancer progression. MEG3 similarly can downregulate mouse double minute 2 homolog (MDM2), and in this way, it can activate p53 as a cell cycle inhibitor and its target genes [51, 52]. Besides, SEMA3B-AS1, LOC100130476, and CTC-276P9.1 are other tumor suppressor lncRNAs downregulated due to hypermethylation in promoters or CpG sites nearby the

Table 1 HOTAIR expression level and function in different cancers

Cancer	Expression level	Function	Refs
Glioma	Upregulated	Mediating HOXA9 actions	[47]
Osteosarcoma	Upregulated	_Increasing DNMT1 expression _Hypermethylation of CDKN2A promoter _miR-126 repression	[74]
SCLC	Upregulated	_DNMT1 and DNMT3b overexpression _Hypermethylation of the HOXA1 promoter region	[75]
HCC	Upregulated	Recruiting EZH2 to the promoter of miR-122	[102]
GIST	Upregulated	_Hyper- or hypomethylating different CpG sites _recruiting the PRC2 to these to CpG sites _Facilitating the interaction between DNMTs, EZH2, and PRC2	[102]

transcription start site. The expression and methylation status in coding genes of these lncRNAs are associated with TNM stages, lymph node metastasis, and patients' survival [53–55].

Leucemia

Myeloma

Like solid tumors, lncRNAs and the changes in their methylation states play an important role in leukemia. This association is studied much more in myeloid leukemia than in lymphoid types. For example, studies show that lncRNA H19, which is involved in BCR-ABL-mediated leukemogenesis, is overexpressed in chronic myelogenous leukemia (CML). Hypomethylation in differentially methylated regions/imprinting control regions (DMR/ICR) is responsible for H19 overexpression and accompanied by H19 expression level can be counted as a biomarker for CML [56]. HOTAIR is also found to be upregulated in CML. A higher methylation level in the HOTAIR promoter is associated with advanced CML [57]. Moreover, MEG3, which has a tumor-suppressive role by targeting miR147 and sponging miR21, shows downregulation and hypermethylation in CML [58]. In AML, MEG3 can prevent leukemogenesis both via the p53 pathway (as a cell cycle inhibitor) and in a p53-independent manner. Significant hypermethylation that is observed in the MEG3 promoter during AML occurs because of TET-2 inactivation or dysregulation in the TET2-WT1-MEG3 regulatory axis. Generally, MEG3 promoter methylation can be a prognostic marker for myeloid malignancies [4, 59, 60]. Neat1, as another tumor lncRNA, can suppress the proliferation, migration, and invasion in AML. Hypermethylation and downregulation of Neat1 promoter, affected by miR-194-5p/DNMT3A axis, lead to AML progression [61]. The BM742401 tumor suppressor is hypermethylated and downregulated in CLL [62].

Lymphoma

In the case of lymphoma and methylation-affected lncRNAs, very few studies have been performed so far. Lymphomas are classified into two categories, Hodgkin's and non-Hodgkin, but each is further subdivided into many subgroups. The most common type of lymphoma is diffuse large B-cell lymphoma (DLBCL) and is non-Hodgkin. A recent study by Zhang at el. has revealed that the tumor suppressor lncRNA NKILA is silenced duo2 to promoter hypermethylation in diffuse large B-cell lymphoma (DLBCL). NKILA is an NF-κB inhibitor so this downregulation leads to cancer progression [63]. In addition to the mentioned cases, other cancers have also been studied in this regard. For example, TMEM51-AS1 and SSTR5-AS1 in laryngeal squamous cell carcinoma, LINC00574 in bladder cancer, GAS5 in osteosarcoma, CXCL12 in thyroid carcinoma, NR_023387 in renal cell carcinoma are other instances of how methylation-related dysregulation in the expression of lncRNAs plays an important role in cancers [64–69]. Accordingly, almost in all of the deadly and prevalent types of cancer, the methylation state of promoter sites (or in some cases methylation of gene body) in lncRNA coding genes exhibits significant changes. This can be used as a diagnostic and prognostic marker and each of these genes and related proteins can be further studied as therapeutic targets.

The effect of DNA methylation on lncRNA

Many lncRNAs are detected to be significantly dysregulated because of the change in the methylation state in the promoter, or in some cases in the body of their coding gene. Aberrant DNA methylation is observed in the genome of various cancers and this can affect the biology of cancer development. Some of the lncRNAs are known for oncogenic or tumor-suppressive roles and can be used as therapeutic targets. Others can be valuable biomarkers, both for their expression level and for promoter methylation state. Therefore, lncRNAs can play a vital role in cancer development. Therefore, we have different examples of these lncRNAs in some of the most important types of cancers (Table 2).

The effect of lncRNA on epigenetics

The effect of lncRNA on DNA methylation processing

LncRNAs have a positive or negative effect on promoter DNA methylation of different genes and genome-wide methylation through various mechanisms (Fig. 1B). They can control biological processes in animals, humans, and plants. LncRNAs, similar to miRs, have oncogenic or tumor-suppressive roles in different cancers [70–73]. As a result, dysregulation of lncRNAs can lead to hyper- or hypomethylation of these genes and direct the related cells and tissues to diverse diseases, especially cancer (Table 3). Various studies have been performed on lncRNAs, which show that the increasing of lncRNAs expression affects the progression of cancer through methylation. DNA methyltransferases, as a group of the important enzymes involved in methylation, can be affected by lncRNAs. One of the most important examples is HOX Transcript Antisense RNA (HOTAIR). The upregulation of HOTAIR mechanistically correlates with hypermethylation of cyclin-dependent kinase Inhibitor 2A (CDKN2A) promoter region through miR-126 (as a negative regulator of DNMT1) repression and increasing DNMT1 expression in osteosarcoma cells [74]. In small cell lung cancer (SCLC), HOTAIR upregulation results in hypermethylation of the homeobox A1 (HOXA1)

Table 2 Effect of DNA methylation on lncRNA expression

lncRNA	Function	Expression level	cancer	Refs
MEG3	Interaction with p53 pathway	Downregulated	BC	[22]
BLAT1	Apoptosis inhibition	Upregulated	BC	[23]
LINC00460	Promoting invasion and migration	Upregulated	CRC	[27]
PVT1	EMT and angiogenesis	Upregulated	Colon adenocarcinoma	[135]
MEG3	Regulation of ATP4B and miR-21 expression	Downregulated	GC	[34]
SOX21-AS1	Sequence-specific DNA binding of RNA polymerase II transcription factor, SOX2 regulation	Upregulated	Cervical cancer	[40]
LINC00592	Transcription and cell integrity	Upregulated	Cervical cancer	[41]
AFAP1-AS1	Upregulating AFAP1, promoting cell migration	Upregulated	NSCLC	[136]
MEG3	ceRNA for miR-9, regulating E-cadherin and FOXO1	Downregulated	ESCC	[51]
H19	BCR-ABL-mediated leukemogenesis	Upregulated	CML	[137]
MEG3	Targeting miR147, sponging miR21	Downregulated	CML	[58]
Neat1	Suppressing proliferation, migration, and invasion	Downregulated	AML	[61]

Table 3 Effect of lncRNA on DNA methylation

lncRNA	Expression level	Target	Cancer	Ref
SNHG14	Upregulated	EPHA7	CRC	[138]
DSCAM-AS1	Upregulated	miR-216b	Colorectal adenocarcinoma	[139]
SNHG3	Upregulated	Med18	GC	[140]
LINC00441	Upregulated	RB1	GC	[56]
LINC00337	Upregulated	TIMP2	NSCLC	[141]
MIR210HG	Upregulated	CACNA2D2	NSCLC	[80]
H19	Upregulated	CDH1	LUAD	[142]
NEAT1	Upregulated	CDH1	OS	[82]
TNRC6C-AS1	Upregulated	STK4	TC	[143]
LincGALH	Upregulated	Gankyrin	HCC	[84]
HAGLR	Downregulated	E2F1	LUAD	[85]
RMST	Downregulated	DNMT3B	Rhabdomyosarcoma	[144]
XIST	Upregulated	p53	Bladder cancer	[145]
AC016405.3	Downregulated	TET2	GBM	[146]
FENDRR	Downregulated	TET2	GC	[147]
MAGI2-AS3	Downregulated	LRIG1	AML	[148]

promoter region via DNMT1 and DNMT3b overexpression [75]. More examples can be mentioned in this regard. Ectopic increase of lnc-AK001058 and DACOR1 in colorectal cancer (CRC) leads to hypermethylation of A-disintegrin and metalloproteinase with thrombospondin motifs 12 (ADAMTS12) promoter and reprogramming genome-wide DNA hypermethylation of many gene promoters like JUN and FOS and consequently, the reduction of Activator protein 1 (AP-1) early response transcription factor through DNMT1, respectively [76, 77]. Studies showed that lncRNA DSCAM-AS1 was upregulated and significantly decreased miR-216b expression via its gene promoter region hypermethylation in colorectal adenocarcinoma tissues compared with marginal tissues [78]. Linc00441 is the other lncRNA that was overexpressed in GC cancerous cells and hypermethylated RB1 and repressed its expression through recruiting DNMT1 to the RB1 promoter [56]. Furthermore, LINC00337 and MIR210HG overexpression results in the hypermethylation and suppression of Tissue Inhibitor of Metalloproteinases 2 (TIMP2) and Voltage-dependent calcium channel subunit alpha2delta-2 (CACNA2D2) as tumor suppressor genes by recruiting and binding DNMT1 to their promoter region in non-small cell lung cancer (NSCLC), respectively [66, 79, 80]. A study performed on lncRNA H19 in lung adenocarcinoma (LUAD) cell lines demonstrated that the upregulation of H19 can hypermethylate the expression of a cell adhesion

molecule, known as E-cadherin (CDH1), by recruiting DNMT3A and DNMT1 to the promoter region of this gene [81]. Additionally, in osteosarcoma cell lines and tissues, CDH1 can be downregulated by binding the G9a-DNMT1-Snail complex to its promoter under the effect of the overexpression of lncRNA NEAT1 [82]. Furthermore, DNMTs can be influenced by lncRNA TNRC6C-AS. Overexpression of lncRNA TNRC6C-AS1 promotes serine/threonine protein kinase 4 (STK4) methylation and downregulation of its expression via recruiting and binding DNMTs to the promoter of this gene and thus more activation of the Hippo signaling pathway in the thyroid carcinoma cells [83]. Also, LincGALH epigenetically can control Gankyrin by modifying the ubiquitination status of DNMT1, thereby deactivating PI3K/Akt/HIF1α and RhoA/ROCK signaling pathways in HCC [84]. In contrast to what was mentioned, several lncRNAs are downregulated in some cancers, which can affect the promoter region methylation of various oncogenes. For instance, downregulation of lncRNA HAGLR (also called HOXD-AS1) as a tumor suppressor lncRNA decreases DNMT1 recruiting to the promoter region of the E2F1 gene, consequently, hypomethylates this gene and increases tumor growth in LUAD tissues [85]. Furthermore, some lncRNAs affect DNA methylation with the normal route. For example, upregulation of lncRNA slincRAD in the early differentiation stages of 3T3-L1 cell hypermethylates p21 gene promoter through DNMT1 recruitment to this region in mouse adipogenesis [86]. Some lncRNAs affect DNMTs expression directly. For instance, lncRNA Rhabdomyosarcoma 2-Associated Transcript (RMST) directly increases the expression of DNMT3B by enhancing HuR as an mRNA stabilizing factor, which binds to the 3' UTR region of DNMT3B mRNA and increases its stability in the Rhabdomyosarcoma both in human and mouse. So this is one of the regulation mechanisms of the global DNA methylation level [87]. The mentioned interactions also had been known between DBCCR1-003, lncRNA PVT1, PAUPAR lncRNA, lncRNA H19, 91H, RP5-833A20.1, ADAMTS9AS2, LINC00470, PCAT-14, ZNFX1-AS 1, lncRNA GIHCG, GAS8-AS1, and DNA methylation in bladder cancer, prostate cancer, uveal melanoma, lung cancer, esophageal squamous cell carcinoma, glioma, esophageal cancer, glioblastoma (GBM), and HCC, respectively [72, 88–98].

LncRNAs affecting methylation via TET family

TET family is the other DNA methylation-related enzymes that can directly or indirectly be modulated by the expression of lncRNAs and affect the DNA methylation of different genes [99]. For example, overexpression of lncRNA X-inactive specific transcript (XIST) decreases the expression of p53 mechanistically through binding to TET1 in bladder cancer [76]. The downregulation of tumor suppressor lncRNA-AC016405.3 and FENDRR as ceRNAs leads to a reduction of TET2 through miR-19a-5p and miR-214-3P overexpression, which targets TET2 gene in the GBM cells and gastric cancer (GC) cell lines, respectively. In this way, lncRNAs can regulate the function of the TET2 enzyme [70, 100]. This association can also be seen among MAGI2-AS3 and DNA demethylation of the LRIG1 promoter mediated by TET2 in adult acute myeloid leukemia (AML) [101].

LncRNAs affecting methylation via EZH2

Several lncRNAs also have been observed with regulatory functions concerning the enhancer of zeste homolog 2 (EZH2). For instance, dysregulation of HOTAIR affects the expression of DNMTs via recruiting EZH2 to the promoter of miR-122 in hepatocellular carcinoma (HCC) [102]. Moreover, in gastrointestinal stromal cell tumors (GIST), increased expression of HOTAIR has a dual role. It can hypermethylate some CpG sites by recruiting the PRC2 to these regions and facilitating the interaction between DNMTs, EZH2, and PRC2. Simultaneously, HOTAIR can hypomethylate some other CpG dinucleotides in GIST [103]. Additionally, the upregulation of lncRNA SNHG14 augments EZH2 expression through the stabilization of its mRNA by interplaying with fused in sarcoma (FUS). It also releases EZH2 mRNA from miR-186-5p-mediated silence, thereby causing hypermethylation of the Ephrin type-A receptor 7 (EPHA7) promoter region as a developmental event mediating gene in CRC cell lines compared to normal colon tissues [104]. Moreover, the ectopic overexpression of lncRNA SNHG3 results in hypermethylation of the Mediator complex subunit 18 (Med18) gene promoter via binding to EZH2 and regulates this neighboring gene expression in GC cell lines [105]. In conclusion, lncRNAs may affect the up-/downregulation of different genes through directly or indirectly modulating DNA methylation and related enzymes, and this can lead to the progression of various cancer-related processes. Therefore, three-dimensional structures of related lncRNAs can be used as therapeutic aims to control methylation status in target cells.

Methylation of lncRNA transcripts

Another type of methylation that occurs in lncRNA transcripts can play an important role in the three-dimensional structure, stability, absorption, and binding of the lncRNA molecule. N6-methyl-adenosine (m6A) is the most abundant posttranscriptional modification in mammalian RNAs, which is carried out by a methyltransferase complex that contains at least one methyltransferase

like 3 (METTL3) subunit. It is a dynamic and reversible regulation that varies in different conditions, for example, in response to cellular stress [106]. This modification is found not only in mRNAs but also in other types of RNAs such as lncRNAs [107]. The functions of m6A and the consequences of dysregulation in this modification are largely unknown because m6a cannot be detected by usual methods and does not affect the base-pairing pattern [106]. The m6A modification exerts direct control over the RNA metabolism, including mRNA processing, mRNA exporting, translation initiation, mRNA stability, and the biogenesis of lncRNA, thereby influencing various aspects of cell function. There are three main groups of proteins in association with m6A: m6A writers, erasers, and readers [108]. Dysregulation in m6a or its related proteins can lead to tumor genesis. Recent studies show that m6a lncRNA modification is associated with different types of cancer. Moreover, m6a may be involved in cancer progression by affecting lncRNA stability and accumulation. For example, lncRNA RP11 is overexpressed in CRC and promotes migration, invasion, and epithelial–mesenchymal transition (EMT). Furthermore, m6A increases RP11 nuclear accumulation and upregulates, thereby preventing Zeb1 (an EMT-related TF) degeneration [109]. Moreover, m6a stabilizes and upregulates LINC00958 in HCC. LINC00958 upregulates hepatoma-derived growth factor (HDGF) expression by sponging miR-3619-5p and helps lipogenesis and cancer progression [110]. Additionally, lncRNA GAS5 facilitates YAP translocation from the nucleus to the cytoplasm and mediates YAP degeneration so it can regulate the Hippo pathway and suppress CRC progression. Finally, m6a modification and m6A reader YTHDF3 lead GAS5 to degeneration and play an oncogenic role in CRC [111]. On the other side, lncRNAs can mediate m6a modification of other RNAs. For example, LINC00470, known as an oncogene, is overexpressed in GC tissue. LINC00470 interaction with m6A writer METTL3 and m6A reader protein YTHDF2 leads PTEN mRNA to degradation [112]. Some of the m6a-associated proteins seem to be involved in different cancers. ALKBH5, an important m6A eraser, is involved in different types of cancers by influencing different lncRNAs. Neat1 plays oncogenic roles such as sponging tumor suppressor miRs and inhibiting the expression of miR-129. In GC, overexpression of ALKBH5 upregulates NEAT1 by decreasing its m6A level. Also, ALKBH5 binds NEAT1 and affects the expression of EZH2, invasion, and metastasis [113]. Furthermore, ALKBH5 protects plasmacytoma variant translocation 1 (PVT1) against degeneration by removing m6A marks and prevents to recognize by the reader protein YTHDF2 in osteosarcoma. This overexpression of PVT1 promotes osteosarcoma cell proliferation [73]. In pancreatic cancer (PC), ALKBH5 and KCNK15-AS1 are both downregulated. lncRNA KCNK15-AS1 inhibits migration and invasion by controlling cell motility. Studies show that KCNK15-AS1 can inhibit PC by demethylating KCNK15-AS1 and may be an important therapeutic target [114]. Insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2) is an m6a reader protein that is demonstrated to have a role in cancer, but the exact mechanism is unknown. It sounds IGF2BP2 interacts with lncRNA DANCR via its m6a marks and together they can have a leading role in PC [76]. Long Intergenic Noncoding RNA for IGF2BP2 Stability (LINRIS) is another lncRNA interacting with IGF2BP2. LINRIS stabilizes IGF2BP2 by blocking K139 ubiquitination. The LINRIS-IGF2BP2-MYC axis has a positive role in CRC progression [115]. Accordingly, N6-methyl-adenosine and related proteins have a crucial role in cancer development. This topic has been less studied compared to other aspects of cancer epigenetics and further studies can lead us to new biomarkers and therapeutic aims.

Interaction of lncRNA and histone modification

Histone modifications like histone acetylation, and methylation, along with others, are epigenetic signatures called epigenetic codes that play vital roles in the regulation of different transcript expressions such as coding and noncoding RNAs (Fig. 2A). Reciprocally, noncoding RNAs, including lncRNAs can mechanistically regulate such histone modifications (Fig. 2B). LncRNAs have important interactions with these modifications and are known as epigenetic modulatory components that can directly or indirectly affect histone modifications and implicate various diseases. The mutual association between histone modifications and lncRNAs is proven. These interactions can lead cells to different cancers [116, 117]. There are few studies on the influence of histone modifications on lncRNAs in different cancers.

Histone acetylation/deacetylation

Tumor suppressor lncRNA BANCR is an example of lncRNAs being regulated via histone deacetylation. BANCR is downregulated in NSCLC tissue in contrast to healthy tissue. This reduction mechanistically happens through overexpression of histone deacetylase (HDAC), especially HDAC3, thereby playing a key role in EMT and metastasis in related cancers [118]. FENDRR is another tumor suppressor lncRNA that is downregulated by histone deacetylation in GC cells compared to normal samples. This downregulation leads to arise of cancerous cells toward malignancy via increasing the levels of fibronectin1 (FN1) and MMP-*2/-9* gene expression [119]. Furthermore, tumor-suppressive LINC01089, which is known as lncRNA Inhibiting Metastasis (LIMT),

is decreased under the influence of histone deacetylation increasing at the related promoter region in the aggressive BC patients and enhances the mammary cells' invasion and metastasis [120]. About histone acetylation, we can mention HOXA-AS3 which is upregulated in A549 cell lines and tissue of LUAD mechanically through its unusual histone acetylation and provides a progression of cancer by forming lncRNA-HOXA6 mRNA duplex and aggregation of HOXA6 expression [121]. Besides, aberrant overexpression of LINC00152 via histone acetylation and consequently an increase of CCNE1, STAT1, STAT3, CREB1, c-MYC, and p38a proteins result in proliferation and poor survival in NSCLC [122]. On the other hand, lncRNAs can affect histone deacetylation and histone acetylation. For example, lncRNA ID2-AS1 is a tumor suppressor lncRNA that can control chromatin modification of its adjacent gene inhibitor of DNA binding 2 (ID2) via blocking HDAC8 binding to the ID2 enhancer. ID2-AS1 is downregulated in HCC cells and tissues [123]. Additionally, overexpression of lncRNA CASC9 can increase H3K27 acetylation in the LAMC2, an upstream inducer of the integrin pathway, and promote ESCC metastasis in association with other factors [124]. Concerning the association with the effect of histone methylation on lncRNA, HOXC-AS3 is a novel oncogenic lncRNA in GC cells that is significantly overexpressed due to the gain of H3K27ac and H3K4 trimethylation (H3K4me3). This abnormal histone methylation of HOXC-AS3 facilitates tumorigenesis via binding to YBX1 [125]. In breast cancer cells, UCA1 lncRNA expression is upregulated by an aberrant decrease of H3K27 trimethylation (H3K27me3) and an aberrant increase of H3K4me3 [126]. Several studies have also been done on the opposite side of this two-way interaction and the effect of lncRNAs on histone methylation. For instance, HOTAIR is a lncRNA whose effect on the various histone modifications was confirmed in some cancers. Studies show that the expression of this lncRNA increases, which regulates histone methyltransferase EZH2, histone H3K27 demethylase JMJD3, and other factors, and therefore, it leads to histone demethylation at various gene loci, e.g., SNAI1, and histone methylation in the others, including PCDH10 in renal cell carcinoma (RCC) tissues compared with non-tumoral tissues [127]. Additionally, HOTAIR can affect cyclin J (CCNJ) gene regulation and the development of cancerous cells by both binding to lysine (K)-specific demethylase 1A (LSD1) and PRC2 on different ends of these chromatin modifiers. Therefore, it causes an imbalance in miR-205 promoter H3K4me3 demethylation and H3K27 methylation and miR inhibition in bladder cancer [128]. Two studies showed that overexpression of lncRNA PVT1 could directly impact histone methylation of ANGPTL4 (angiopoietin-like 4) promoter region and indirectly downregulate EZH2 through miRNA-526b targeting at miRNA-526b/EZH2 loop in cholangiocarcinoma (CCA) and NSCLC cells, respectively [129, 130]. Moreover, lncRNAs can influence gene histone methylation by interacting with MBD1. For instance, H19 lncRNA has an important role in histone methylation of some genes such as paternally expressed gene 1 (Peg1), insulin-like growth factor 2 (Igf2), and solute carrier family 38 member 4 (Slc38a4) through recruiting MBD1 and the other histone-modifying enzymes to these regions [131].

Multipole kinds of modifications

According to the studies, some lncRNAs are related to more than one type of histone modification in some types of cancer. For example, linc00460 lncRNA has an oncogenic role in ESCC and is overexpressed through many histone modifications, including histone H3 acetylation, H3K27Ac, H3K4Me3, and H3K4Me1 in collaboration with the binding of many transcription factors like P300, CEBPB, Jun, GATA2, Fos, etc. to its promoter region [132]. Moreover, HOTAIR plays an oncogenic role in BC in vivo and in vitro mediated by the effect of estradiol (E2) on its promoter's estrogen response elements (EREs) together with CBP/p300, histone methylases MLL3 and MLL1, histone H3K4-trimethylation, and histone acetylation. Therefore, this lncRNA can be affected by multihistone modification factors [133]. Reciprocally, PRC2 recruitment to E-cadherin promoter, reduction in H3K27 acetylation, increase in H3K27 methylation, and changing of histone acetylation to methylation in EMT of GC are other effects of HOTAIR on the histone modification [134]. As it comes from these studies, the interaction between histone modification and lncRNAs is critical to find out how some cancers take place in different cells and tissue types without mutation in the lncRNA gene and investigate the transcriptional regulation roles of lncRNAs in a specific condition, which will improve our understanding of lncRNA genes.

Future perspective

The role of lncRNAs in different diseases has recently received special attention. There are also special databases dedicated to this topic such as the lncRNA disease database and lnc2cancer. Although many studies have been operated on how lncRNAs are involved in tumor genesis and epigenetics of cancer, there are still many unknown aspects in this field. There are other lncRNAs, which may be associated with cancer epigenetics and can be novel biomarkers. As declared above, the epigenetic state of a lncRNA coding gene can be a more reliable biomarker than the expression level of that lncRNA in some cases. In addition, better insight into mechanisms can

show us new potential therapeutic targets. For example, mentioned lncRNAs or related proteins can be directly or indirectly targeted for therapy. Correspondingly, siRNAs, antisense RNAs, aptamers, and miRs can be used to suppress oncogenic lncRNAs or methylation inducer substances that can be recruited to induce methylation in promoter regions and prevent transcription of these oncogenes in the first place. On the contrary, demethylase elements can be used to upregulate tumor suppressor lncRNAs by eliminating methyl groups from their promoter. Topics such as N6 methyl adenosine are worthy of more attention. How other readers and eraser proteins interact with lncRNAs and other lncRNA undergoing m6a modification needs to be investigated. We tried to have an overview of what is done so far and what needs to be more focused on.

Conclusion

LncRNAs, despite being noncoding RNAs, can play key roles in the normal function of the cells and different diseases such as cancer. The expression levels of lncRNAs can be associated with cancer's stage, grade, prognosis, and outcome. They can be involved in cancer progression or prevention via their interactions with different epigenetic mechanisms, including DNA methylation, histone methylation, histone acetylation, and histone deacetylation. In other words, the epigenetic regulation of lncRNAs and lncRNA-associated genes makes an indirectly epigenetic-mediated regulation of tumorigenic genes that occurred as the network in cancer progression. Given the importance of these associations presented in this review, more studies and supplementary experiments may shed the light on the cancer complexity and help find innovative approaches for the management of cancer in different stages and levels.

Abbreviations

ADAMTS12	A-Disintegrin and metalloproteinase with thrombospondin motifs 12
AML	Adult acute myeloid leukemia
AP-1	Activator protein 1
BC	Breast cancer
BLBC	Basal-Like breast cancer
BLAT1	Basal-Like breast cancer Associated Transcript1
CACNA2D2	Calcium channel subunit alpha2delta-2
CCA	Cholangiocarcinoma
CCNJ	Cyclin J
CDKN2A	Cyclin-dependent kinase Inhibitor 2A
ceRNA	Competing for endogenous RNA
CML	Chronic myelogenous leukemia
CRC	Colorectal cancer
DNMT	DNA methyltransferase
E2	Estradiol
EMT	Epithelial–mesenchymal transition
EPHA7	Ephrin type-A receptor 7
EREs	Estrogen response elements
ESCC	Esophageal squamous cell carcinoma
EZH2	Enhancer of zeste homolog 2
FN1	Fibronectin1
FUS	Fused in sarcoma
GBM	Glioblastoma
GC	Gastric cancer
GIST	Gastrointestinal stromal cell tumors
H3K4me3	H3K4 trimethylation
HCC	Hepatocellular carcinoma
HDAC	Histone deacetylase
HDGF	Hepatoma-derived growth factor
HOTAIR	HOX Transcript Antisense RNA
HOXA1	Homeobox A1
HPV	Human papillomavirus
ID2	Inhibitor of DNA binding 2
Igf2	Insulin-like growth factor 2
LIMT	LncRNA Inhibiting Metastasis
lncRNA	Long noncoding RNAs
LSD1	Lysine (K)-specific demethylase 1A
LUAD	Lung adenocarcinoma
MBDs	Methyl-CpG-binding domains
MDM2	Mouse double minute 2 homolog
MeCP2	Methyl-CpG-binding protein 2
Med18	Mediator complex subunit 18
MEG3	Maternally expressed gene 3
METTL3	Methyltransferase like 3
miR	MicroRNA
MMP	Matrix metalloproteinase
NSCLC	Non-small cell lung cancer
PC	Pancreatic cancer
Peg1	Paternally expressed gene 1
PRC2	Polycomb repressive complex 2
PVT1	plasmacytoma variant translocation 1
RCC	Renal cell carcinoma
RMST	Rhabdomyosarcoma 2-associated transcript
SCLC	Small cell lung cancer
Slc38a4	Solute carrier family 38 member 4
STK4	Serine/threonine protein kinase 4
TET	Ten-eleven translocation
TIMP2	Tissue Inhibitor of Metalloproteinases 2
UCA1	Urothelial carcinoma-associated 1
XIST	X-inactive specific transcript

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Author contributions

MR and MA designed the study and drafted the manuscript. SH, MS-K, and MP were involved in data collection. ZF, FS, and DR critically revised the manuscript for important intellectual contents and MA and VT supervised the study. All listed authors read and approved the final manuscript.

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Availability of data and materials

Please contact the corresponding author for data requests.

Declarations

Ethics approval and consent to participate

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Competing interests

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