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Review

Long Non-Coding RNAs in Cancer: Mechanistic Roles Across Core Hallmarks, AI-Enabled Discovery, and Precision Oncology

Pejman Hosseinzadeh[1,2+], Elaheh Gheybi[1+], Mehdi Rostami[3,4+], Ghazaleh Doostparast Torshizi[5], Saeedeh Askarian[5,6], Sobhan Pouramini[3], Mehraneh Nouri[7], Mohammad Soukhtanloo [1,8*], Ramin Raoufinia[5,9*]

[1]*Department of Clinical Biochemistry, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.*
[2]*Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran.*
[3]*Molecular and Medicine Research Center, Arak University of Medical Sciences, Arak,Iran.*
[4]*Clinical Research Development Unit of Amiralmomenin Hospital, Arak University of Medical Sciences, Arak, Iran.*
[5]*Noncommunicable Diseases Research Center, Neyshabur University of Medical Sciences, Neyshabur, Iran.*
[6]*Department of Medical Biotechnology, Neyshabur University of Medical Sciences, Neyshabur, Iran.*
[7]*Department of Medical Genetics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.*
[8]*Pharmacological Research Center of Medicinal Plants, Mashhad University of Medical Sciences, Mashhad, Iran.*
[9]*Healthy Ageing Research Centre, Neyshabur University of Medical Sciences, Neyshabur, Iran.*

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Abstract

Introduction: Cancer pathogenesis is characterized by the acquisition of hallmark capabilities that collectively enable tumor initiation, progression, and metastatic dissemination. Among the diverse regulatory elements implicated in these processes, long non-coding RNAs (lncRNAs) have emerged as pivotal modulators of cancer biology. Through multilayered regulation of gene expression, chromatin remodeling, epigenetic modification, and signal transduction pathways, lncRNAs orchestrate key oncogenic and tumor-suppressive networks. Accumulating evidence implicates representative lncRNAs, including MALAT1, MEG3, GAS5, HOTAIR, TERRA, XIST, and UCA1, in the context-dependent regulation of proliferation, cell-death responses, telomere maintenance, angiogenesis, and invasion and metastasis.

Aim: This narrative review aims to critically synthesize current evidence regarding the mechanistic roles of key lncRNAs across established cancer hallmarks and to delineate their contributions to oncogenic and tumor-suppressive regulatory circuits. Furthermore, the review examines artificial intelligence (AI)-based approaches to lncRNA identification, functional annotation, and disease-association prediction, with attention to their evaluated tasks, limitations, and requirements for biological validation.

Conclusion: Current studies implicate lncRNAs in several cancer-associated processes through transcriptional, post-transcriptional, and chromatin-related regulation. Their context-dependent effects support further investigation as candidate biomarkers and therapeutic targets. However, experimental findings, patient associations, and clinical validation represent different types of evidence. AI methods can assist computational annotation and candidate prioritization, while molecular mechanisms and clinical usefulness require independent confirmation.

+ Contributed equally to this study.

* **Corresponding Author:**

Mohammad Soukhtanloo
E-mail: soukhtanloom@gmail.com

Ramin Raoufinia
E-mail: r.raoofi69@gmail.com

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1. INTRODUCTION

The lncRNAs are conventionally defined as transcripts longer than 200 nucleotides with limited protein-coding potential. The length threshold is operational and does not establish biological function [1]. These macromolecules function as key regulatory agents, influencing diverse cellular mechanisms. Their roles include recruiting chromatin-remodeling complexes to specific genomic loci , acting as molecular scaffolds for ribonucleoprotein assembly, modulating transcriptional activity , and regulating gene expression post-transcriptionally [2]. Consequently, lncRNAs are established as critical modulators of gene expression across epigenetic, transcriptional, and post-transcriptional levels, interacting with a wide array of cellular components [3].

In the context of cancer, a disease state characterized by unchecked proliferation and invasive potential, lncRNAs function as pivotal drivers or suppressors of tumorigenesis and may act as either oncogenes or tumor suppressors [4]. Aberrant expression of specific lncRNAs is frequently triggered by oncogenic stimuli, and the resulting transcripts play significant roles in establishing and maintaining the malignant phenotype. The critical role of lncRNAs in regulating diverse cellular processes strongly influences cellular fate. Therefore, cancer development may be promoted through lncRNA-mediated regulation of microRNAs (miRNAs) or through direct modulation of gene expression [5].

The conceptual framework of cancer hallmarks provides a systematic approach for understanding the disease's underlying mechanisms. Targeting these shared capabilities is essential for developing novel, broadly effective diagnostic and therapeutic strategies. These hallmark capabilities are regulated through interconnected signaling networks, including PI3K/AKT/mTOR, NF-κB, Wnt/β-catenin, Notch, Hippo/YAP–TAZ, and p53-associated pathways [6, 7]. A promising frontier in this effort involves elucidating the role of non-coding RNAs, particularly lncRNAs, in regulating these core hallmarks. This review synthesizes current knowledge on the mechanisms by which lncRNAs influence the hallmark traits of cancer, with the aim of highlighting their potential as targets for advancing cancer diagnosis and therapy. To provide a comprehensive overview, this review first summarizes the biological characteristics and molecular functions of lncRNAs, followed by a hallmark-oriented discussion of their roles in tumorigenesis. Finally, recent advances in AI-based approaches for lncRNA identification, functional annotation, and disease association analysis are critically discussed in the context of precision oncology.

1.1 Literature Search Strategy

A literature search was conducted in PubMed, Scopus, and Web of Science and was updated on 10 August 2026. The search strategy was developed around three main concept groups. The first group included the terms long non-coding RNA, lncRNA, lincRNA, and long intergenic non-coding RNA. The second group included cancer, tumor, tumor, neoplasm, carcinoma, and malignancy. The third group included cancer-related processes and analytical approaches, including proliferation, cell death, apoptosis, ferroptosis, pyroptosis, autophagy, angiogenesis, metastasis, invasion, epithelial–mesenchymal transition, EMT, telomere maintenance, artificial intelligence, machine learning, deep learning, transformer models, graph neural networks, multi-omics, single-cell transcriptomics, precision oncology, and lncRNA–disease associations. These terms were combined using the Boolean operators AND and OR and were adapted to the search functions of each database. Additional searches were performed by combining lncRNA with cancer hallmarks, drug resistance, precision oncology, and computational prediction. Original research articles, mechanistic studies, computational studies, and relevant review articles published in English were considered. Articles unrelated to lncRNAs or cancer, conference abstracts without sufficient information, and studies that did not provide relevant biological or computational evidence were excluded. Duplicate records were removed before screening. Titles and abstracts were screened for relevance, and the full texts of potentially eligible articles were subsequently assessed. Articles that did not directly support the relevant mechanistic or computational statements were excluded from the final synthesis. The reference lists of eligible articles were also examined to identify additional relevant studies. As this article was prepared as a narrative review, no formal meta-analysis or quantitative risk-of-bias assessment was performed.

2. LNCRNA EXPRESSION AND FUNCTION

In the transcriptome analysis by Cabili and colleagues, lower expression and greater tissue specificity were observed for lincRNAs than for protein-coding genes. Tissue-specific expression was reported for 78% of lincRNAs and approximately 19% of coding genes in the analysed dataset [8]. Greater inter-individual expression variability was subsequently observed for lncRNAs across several human tissues [9]. The regulatory potential of lncRNAs, first suggested by their distinct expression patterns, subcellular localization, and roles in development in the early 1990s, is now well-established [10]. They employ diverse molecular mechanisms: as miRNA decoys or "sponges," they sequester miRNAs, attenuating their repressive effects on target mRNAs [11]; as guides, they direct chromatin-modifying enzymes to specific genomic targets in cis (local) or trans (distinct chromosomal regions) [12]; and as scaffolds, they nucleate the assembly of multi-protein complexes involved in nuclear processes such as transcriptional regulation and chromatin remodeling [13]. Altered miRNA expression has been associated with tumor development, invasion, metastasis, and treatment response in specific cancer settings [14].

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3. The Impact of lncRNAs on the Hallmark Traits of Cancer

Tumor development requires the acquisition of distinct hallmark capabilities, including sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, replicative immortality, induction of angiogenesis, and activation of invasion and metastasis. A growing body of evidence indicates that various functional lncRNAs regulate oncogenesis by modulating one or more of these core traits. The major regulatory mechanisms mediated by representative lncRNAs are schematically illustrated in Fig. 1. In addition, the hallmark-associated functions, molecular targets, and biological effects of key lncRNAs are systematically summarized in **Table 1.**

Throughout this review, evidence is identified by study type: in vitro evidence refers to experiments in cultured cell lines or primary cells; in vivo/preclinical evidence refers to animal experiments; human-associated evidence refers to measurements or associations in patient tissues, blood samples, or observational cohorts; and clinical validation refers to independently validated clinical performance or utility in the intended setting. Computational predictions are identified separately. These categories describe the source of evidence and are not a formal risk-of-bias score. The presence of patient samples does not, by itself, establish the molecular mechanism or clinical effectiveness of a lncRNA-directed intervention.

3.1 Sustaining Proliferative Signaling and Evading Growth Suppressors

Functional effects of individual lncRNAs should be interpreted within the cancer type, cell compartment, and experimental conditions in which they were observed. For example, MEG3 inhibited tube formation in ovarian tumor-derived endothelial cells but promoted angiogenesis in glioblastoma stem-cell models. Contrasting findings have also been reported for MALAT1 in breast cancer systems. These observations support context-specific descriptions of lncRNA activity and make uniform oncogenic or tumor-suppressive labels insufficient. The following sections therefore identify the model and outcome underlying each example [15-18]. Dysregulated proliferation, driven by alterations in cell cycle-associated proteins, is fundamental to cancer initiation and progression [19]. MALAT1 has been implicated in cancer-related processes through several regulatory mechanisms, but the direction of its effect varies across experimental systems. The examples discussed here are therefore interpreted according to their cellular models and measured outcomes. Malat1 expression was reduced during all-trans retinoic acid (ATRA) -induced differentiation of mouse EML cells. Higher expression was also detected in early-stage LRH progenitors than in late-stage LRB progenitors. EML cell proliferation was reduced after Malat1 depletion. These findings were obtained in mouse hematopoietic models and should not be interpreted as evidence from acute myeloid leukemia (AML) patients[20]. Reduced proliferation, increased apoptosis, and greater cytarabine sensitivity were observed after MALAT1 knockdown in AML cells. These effects were linked to increased miR-96 expression [21]. Repression of a minimal p53 promoter region by MALAT1 was reported in human lung adenocarcinoma cells [22]. In PC3 and DU145 prostate cancer cells, MEG3 overexpression reduced Cyclin D1 expression, induced G0/G1 arrest, and shifted apoptosis-associated proteins toward increased Bax and caspase-3 activation and reduced Bcl-2. Reduced growth was also observed in PC3 xenografts. These findings describe the tested prostate cancer models rather than a universal MEG3 mechanism [23]. In colorectal cancer cell models, vitamin D/VDR signaling increased MEG3 expression, while MEG3 overexpression promoted ubiquitin-dependent c-Myc degradation and suppressed aerobic glycolysis [24]. Other lncRNAs contribute to proliferative signaling through diverse mechanisms:

In gastric cancer models, XIST promoted cell growth and invasion through the miR-497/MACC1 axis. Functional experiments supported this regulatory relationship, while elevated XIST expression in patient tumors were associated with adverse clinicopathological features [25]. In gastric cancer cell models, RMRP was reported to regulate the miR-206/Cyclin D2 axis and support proliferation. This functional finding should be distinguished from the tissue-expression pattern, which was reduced in many patient tumors in the same report [26].

In colorectal cancer models, FEZF1-AS1 was associated with PCK2 protein regulation. FEZF1-AS1 deletion reduced PCK2 protein without a corresponding reduction in its mRNA, and PCK2 re-expression partially restored proliferation and tumor growth. The study did not resolve how FEZF1-AS1 regulated PCK2 protein abundance [27]. FAM83H-AS1 is upregulated in colorectal cancer (CRC) and promotes proliferation by activating the Notch1 signaling pathway [28]. In gastric cancer models, GAS5 overexpression inhibited proliferation and invasion and promoted apoptosis through the miR-106a-5p/Akt/mTOR pathway. miRNA rescue experiments supported this regulatory axis, and tumor-growth effects were examined in mouse xenografts [29].

In colorectal cancer cells, CRNDE interacted with hnRNPA2B1 and reduced its ubiquitination, increasing protein stability. This supported KRAS mRNA nuclear export and translation and was linked to downstream MAPK signaling. Functional perturbation experiments supported the CRNDE–hnRNPA2B1–KRAS relationship [30].

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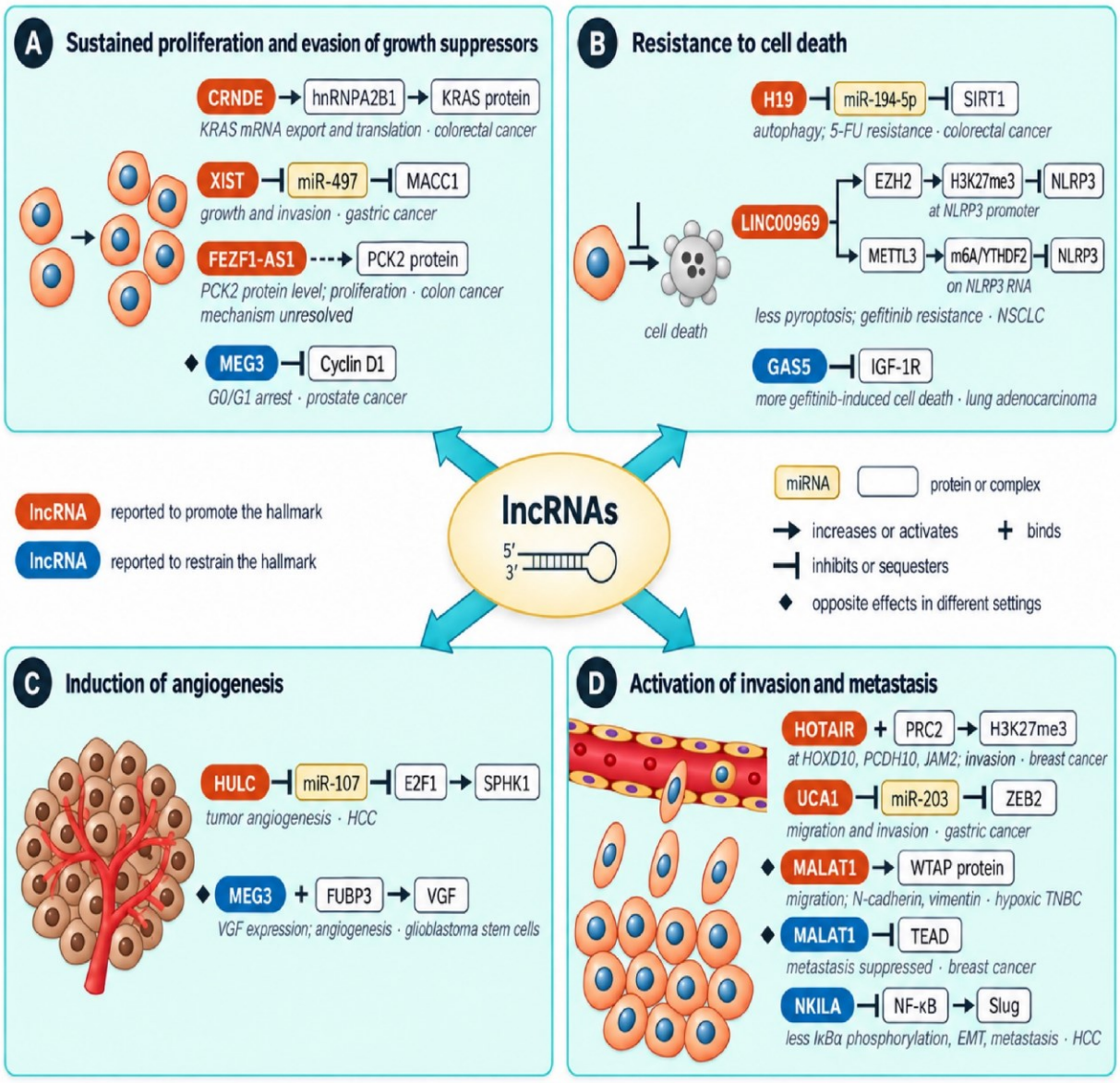

Figure 1. Representative lncRNA-associated regulatory axes in four cancer hallmarks. (A) Sustained proliferation and evasion of growth suppressors. (B) Resistance to cell death. (C) Induction of angiogenesis. (D) Activation of invasion and metastasis. Orange labels mark lncRNAs reported to promote the hallmark. Blue labels mark lncRNAs reported to restrain it. Arrows indicate an increase or activation. Blunt-ended lines indicate inhibition or sequestration. A plus sign indicates binding. Diamonds mark lncRNAs for which opposite effects were reported in different settings. The outcome and the experimental setting are given in italics below each axis. Each axis is shown as reported in the cited experimental model. No axis represents a clinically validated intervention. Telomere maintenance is discussed in the text and is not shown.

Abbreviations: 5-FU, 5-fluorouracil; CRNDE, colorectal neoplasia differentially expressed; E2F1, E2F transcription factor 1; EMT, epithelial–mesenchymal transition; EZH2, enhancer of zeste homolog 2; FEZF1-AS1, FEZF1 antisense RNA 1; FUBP3, far upstream element-binding protein 3; GAS5, growth arrest-specific 5; H3K27me3, trimethylation of histone H3 lysine 27; HCC, hepatocellular carcinoma; hnRNPA2B1, heterogeneous nuclear ribonucleoprotein A2/B1; HOTAIR, HOX transcript antisense RNA; HOXD10, homeobox D10; HULC, highly upregulated in liver cancer; IGF-1R, insulin-like growth factor 1 receptor; IκBα, NF-κB inhibitor alpha; JAM2, junctional adhesion molecule 2; KRAS, Kirsten rat sarcoma viral oncogene homolog; lncRNA, long non-coding RNA; MACC1, metastasis-associated in colon cancer 1; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MEG3, maternally expressed gene 3; METTL3, methyltransferase-like 3; miRNA, microRNA; NF-κB, nuclear factor kappa B; NKILA, NF-κB-interacting lncRNA; NLRP3, NLR family pyrin domain-containing 3; NSCLC, non-small cell lung cancer; PCDH10, protocadherin 10; PCK2, phosphoenolpyruvate carboxykinase 2; PRC2, Polycomb repressive complex 2; SIRT1, sirtuin 1; SPHK1, sphingosine kinase 1; TEAD, TEA domain transcription factor; TNBC, triple-negative breast cancer; UCA1, urothelial carcinoma-associated 1; VGF, VGF nerve growth factor inducible; WTAP, Wilms tumor 1-associated protein; XIST, X-inactive specific transcript; ZEB2, zinc finger E-box-binding homeobox 2.

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Increased URHC expression was reported in HCC. Cell proliferation and apoptosis were regulated through ZAK-associated ERK/MAPK signaling in the tested models [31].

Critical perspective and future directions:

Studies of FEZF1-AS1 and CRNDE illustrate different levels of mechanistic resolution within colorectal cancer. FEZF1-AS1 depletion reduced PCK2 protein abundance, and PCK2 re-expression partially restored proliferation and tumor growth; however, the mechanism regulating PCK2 protein levels remained unresolved. In contrast, the CRNDE study linked hnRNPA2B1 stabilization to KRAS mRNA export and translation. These perturbation and rescue experiments provide stronger functional evidence than expression–outcome associations alone, while leaving the feasibility of therapeutically targeting either pathway in patients unestablished [27, 30].

3.2 lncRNAs and Resistance to Cell Death

Non-coding RNAs, including lncRNAs, have been implicated in the regulation of ferroptosis [32]. The specific examples of lncRNA-associated apoptosis, autophagy-related treatment resistance, and pyroptosis are discussed below. Reduced GAS5 expression was associated with clinicopathological features in lung adenocarcinoma tissues. Separately, GAS5 overexpression enhanced gefitinib-induced cell death in EGFR-wild-type, KRAS-mutant A549 cells and improved the experimental treatment response in mouse xenografts. The tissue findings were observational, whereas the functional and treatment effects were demonstrated in preclinical models [33].

In HCC models, NKILA overexpression reduced migration, invasion, and experimental lung colonization through NF-κB/Slug-associated EMT regulation, while having little effect on proliferation in the tested cells. Higher NKILA expression was associated with favourable survival in the patient analysis [34]. In tumor-specific T cells, NKILA was reported to increase susceptibility to activation-induced cell death and facilitate tumor immune evasion. This immune-cell finding should be distinguished from the metastasis-suppressive effects observed in HCC cells [35].

Lower TUSC7 expression was associated with poorer overall survival in the esophageal squamous cell carcinoma (ESCC) cohort. In ESCC experimental models, TUSC7 overexpression reduced proliferation and chemotherapy resistance through miR-224/DESC1 regulation [36]. In colorectal cancer models, H19 promoted 5-fluorouracil resistance through the miR-194-5p/SIRT1 axis and increased autophagy-associated survival signaling. These findings were supported by cell-based experiments and patient-associated analyses, but they did not establish clinical treatment efficacy [37, 38].

HOTAIR is upregulated in a wide variety of human cancers. Its dysregulation has been associated with proliferation, invasion, and metastasis [39].

In gefitinib-resistant lung cancer cells, CK2-dependent phosphorylation of topoisomerase IIα at serine 1106 was induced by an ecto-ATP synthase inhibitor. GAS5 expression was subsequently increased, and the downstream p53 pathway was activated [40].

In gefitinib-resistant EGFR-mutant lung cancer models, LINC00969 repressed NLRP3 through two distinct processes: EZH2-associated H3K27 trimethylation at the NLRP3 promoter and METTL3-dependent N6-methyladenosine (m6A) modification of NLRP3 RNA in an m6A–YTHDF2-dependent manner. These transcriptional and post-transcriptional effects reduced pyroptotic responses [41].

Critical perspective and future directions:

The H19 and LINC00969 studies concern distinct resistance mechanisms and should not be treated as interchangeable evidence of cell-death regulation. H19 supported 5-fluorouracil resistance through SIRT1-associated autophagy in colorectal cancer cells, whereas LINC00969 suppressed NLRP3-associated pyroptosis in gefitinib-resistant lung cancer models. The H19 report combined cell experiments with patient-associated findings; the LINC00969 report also included a mouse treatment experiment using intratumoral siRNA delivery. These differences affect translational interpretation, particularly because local delivery in a xenograft does not establish the feasibility of systemic treatment [38, 41].

3.3 LncRNAs and Angiogenesis

As solid tumors enlarge, their metabolic demands can exceed the capacity of diffusion from existing vessels, making vascular supply an important determinant of continued growth and progression. Angiogenesis can support tumor growth by increasing vascular supply and partially alleviating limitations in oxygen and nutrient delivery [42]. Given its central role in oncogenesis, angiogenesis represents a critical therapeutic target, with lncRNAs emerging as key modulators of this process [43]. Angiogenesis is primarily regulated by the vascular endothelial growth factor (VEGF) family and its receptors, including the tyrosine kinase receptors VEGFR1 and VEGFR2, as well as neuropilins (NRPs) [44]. VEGF binding induces receptor dimerization and tyrosine phosphorylation, activating intricate intracellular signaling cascades that promote new blood vessel formation. VEGFR3 is primarily involved in lymphangiogenesis. Tumor hypoxia serves as a major physiological trigger, stabilizing hypoxia-inducible factors (HIF-1 and HIF-2) that transcriptionally activate pro-angiogenic genes, promoting

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the migration of endothelial tip cells from existing vessels [45, 46]. lncRNAs regulate multiple facets of this signaling axis, from modulating VEGF-VEGFR interactions to fine-tuning downstream pathways [47].

In ovarian tumor-derived endothelial cells, MEG3 overexpression inhibited tube formation through miR-376a/RASA1 regulation. YBX1 competed with miR-376a for MEG3 binding and modified this regulatory response. A different effect was reported in glioblastoma stem cells, where MEG3 supported FUBP3-dependent VGF expression and angiogenic responses. Conditioned-medium experiments and orthotopic mouse tumors supported this mechanism, while human expression analyses provided associated clinical observations. In HCC models, HULC regulated angiogenesis through the miR-107/E2F1/SPHK1 pathway. Experiments included hepatoma-cell conditioned medium applied to endothelial cells, chick chorioallantoic membranes, and mouse xenografts. Human HCC tissues provided expression correlations, which should be distinguished from the experimental mechanism [15, 16, 48].

In an in vitro blood–tumor barrier model, XIST knockdown increased barrier permeability and reduced endothelial migration and tube formation. The study implicated miR-137, FOXC1, tight-junction regulation, and CXCR7-associated angiogenic responses. These findings arose from an endothelial–glioma co-culture system. In gastric cancer, PVT1 was reported to promote angiogenesis through the STAT3/VEGFA axis [49, 50].

Critical perspective and future directions:

MEG3 provides a clear example of why the cellular compartment matters when interpreting angiogenic effects. It inhibited tube formation in ovarian tumor-derived endothelial cells but promoted angiogenesis through FUBP3-dependent VGF expression in glioblastoma stem-cell models. The latter study also included orthotopic mouse tumors. These findings concern different cellular compartments and regulatory partners; they do not establish that cancer type alone explains the opposing effects. Endothelial tube formation, tumor vascularization in mice, and patient expression–survival associations should therefore be interpreted as distinct outcomes [15, 16].

3.4 lncRNAs in Activating Invasion and Metastasis

Metastasis is a multi-step process wherein cancer cells disseminate from the primary tumor and colonize distant organs. A pivotal event in this cascade is the epithelial-to-mesenchymal transition (EMT), which confers increased migratory and invasive properties upon epithelial cancer cells [51]. lncRNAs are crucial regulators of metastasis, influencing EMT, dissemination, and colonization through diverse molecular mechanisms.

In breast cancer models, HOTAIR overexpression altered PRC2 occupancy and H3K27 trimethylation and repressed genes including HOXD10, JAM2, and PCDH10. PRC2 depletion reduced the HOTAIR-associated invasive phenotype, and mouse experiments supported increased metastatic colonization. These results support chromatin-associated invasion and metastasis effects in the tested systems [52]. In gastric cancer models, UCA1 regulated the miR-203/ZEB2 axis and promoted migration and invasion. Binding-site reporter and rescue experiments supported this relationship, while a tail-vein mouse model examined metastatic colonization [53].

In the TGF-β-induced EMT model examined by Li and colleagues, ANCR attenuated EMT-associated changes by reducing RUNX2 expression. TGF-β-associated ANCR repression involved promoter histone deacetylation. ANCR expression also reduced experimental lung colonization by breast cancer cells [54]. TP73-AS1 forms a positive feedback loop with ZEB1. It sponges miR-200a to increase ZEB1 expression, while ZEB1, in turn, binds to the TP73-AS1 promoter to enhance its transcription, collectively driving BC cell migration and invasion [55].

In breast cancer models, ITGB2-AS1 enhanced cell migration and invasion by increasing the expression of its sense gene ITGB2 and activating integrin-associated focal adhesion kinase signalling [56].

In hypoxic triple-negative breast cancer cells, MALAT1 depletion reduced WTAP protein despite increased WTAP mRNA. WTAP depletion reduced HIF1-associated responses, migration, and expression of N-cadherin and vimentin. These results illustrate why oxygen conditions and protein-level measurements can change the interpretation of a lncRNA-associated regulatory pathway [18]. In breast cancer models, MALAT1 bound and inhibited TEAD, preventing its association with YAP and target gene promoters. Genetic inactivation of Malat1 increased lung metastasis, whereas restoration of its expression reversed this effect [17]. In renal cell carcinoma models, MALAT1 silencing increased E-cadherin expression and reduced H3K27me3 at the E-cadherin promoter, consistent with EZH2-associated transcriptional repression [57].

SNHG7 is upregulated in colon cancer, particularly in invasive cases. It promotes CRC cell proliferation, migration, invasion, and EMT. GALNT1 was upregulated through miR-216b sponging by SNHG7. Tumorigenesis and liver metastasis of SW480 cells were enhanced by SNHG7 overexpression in vivo [58]. In summary, lncRNAs regulate metastasis through diverse and interconnected mechanisms, often centered on the control of EMT and integrin signaling, positioning them as potential therapeutic targets for advanced disease.

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Critical perspective and future directions:

Contrasting MALAT1 findings highlight the importance of both experimental design and biological endpoint. Genetic inactivation and restoration experiments supported a metastasis-suppressive function in breast cancer models, whereas a later study implicated the MALAT1–WTAP axis in hypoxia-associated migration and EMT-related changes in triple-negative breast cancer cells. The restoration experiments strengthen attribution to MALAT1, while migration and EMT measurements address only selected components of metastatic progression. Differences in perturbation strategy, cellular background, and oxygen conditions should therefore be considered when comparing these reports [17, 18].

3.5 lncRNAs in Telomere Maintenance and Replicative Immortality

Telomeric repeat-containing RNA (TERRA) represents a class of lncRNAs transcribed from the subtelomeric regions of chromosomes. TERRA is used here as a representative telomere-associated lncRNA because its experimentally studied functions connect telomeric RNA–DNA hybrids with telomerase-associated and recombination-dependent maintenance. The section focuses on these mechanisms rather than providing an exhaustive catalogue of all lncRNAs that influence telomere biology [59-61]. These transcripts play a crucial role in regulating telomere chromatin architecture and maintenance, influencing both telomerase-mediated elongation and homology-directed repair mechanisms [62]. TERRA localizes to chromosome ends via its UUAGGG repeats. In cultured human cells, RAD51 and BRCA2 supported recruitment of TERRA to telomeres through R-loops formed in trans. Recruitment favoured short telomeres, and TERRA-associated telomere fragility was counteracted by RNase H1 and TRF1 [59]. In 176 paired HCC specimens, lower TERRA expression was associated with poorer patient outcomes. Growth and metastasis of HCC cells were promoted by TERRA downregulation in vitro and in vivo. The opposite effect was observed after TERRA upregulation. Telomerase activity and telomere elongation were increased by TERRA downregulation. The tumor-promoting effect was reversed by the telomerase inhibitor TMPyP4. The human findings were correlational, while the functional conclusions arose from experimental models [60]. In alternative lengthening of telomeres (ALT)-positive models, METTL3-dependent m6A modification supported TERRA interaction with hnRNPA2B1 and telomeric R-loop formation. The study distinguished impaired TERRA localization from changes in overall RNA abundance and linked METTL3 depletion to reduced growth of ALT-positive neuroblastoma xenografts. Pharmacological experiments were conducted in cultured cells and spheroids. These findings support a preclinical role for the METTL3–TERRA pathway in ALT maintenance [61]. In 50 patients with meningioma and 44 healthy controls, free and DNA-hybridized TERRA (h-TERRA) were measured before surgery and 6 months after surgery. A moderate positive correlation was found between postoperative blood h-TERRA and postoperative tumor volume ($r = 0.38$, $p = 0.008$). The cohort was small and follow-up was short. This provides a human observational example of TERRA-related monitoring, while independent validation is required before clinical biomarker performance can be established [63].

Critical perspective and future directions:

TERRA-associated findings differ according to the telomere-maintenance mechanism examined. The HCC study linked reduced TERRA to telomerase activity and tumor-associated phenotypes, whereas ALT-positive models implicated modified TERRA in telomeric R-loop formation and maintenance. TERRA abundance and telomere localization are therefore distinct variables, and an expression measurement alone may not describe its functional state. Human associations and experimental perturbations support further investigation but do not establish a uniform therapeutic direction across cancers [60, 61].

Although extensive experimental investigations have clarified the involvement of lncRNAs in multiple cancer hallmarks, the rapidly increasing volume and complexity of transcriptomic and multi-omics datasets have created substantial analytical challenges. Computational approaches can assist the prioritization of lncRNAs and candidate disease associations for further investigation. The broader use of artificial intelligence with transcriptomic and multi-omics data has also been discussed in leukemia research, particularly for disease classification, prognosis, and treatment selection. Their outputs should be interpreted according to the prediction task and the evidence used for evaluation [64, 65].

Collectively, these findings indicate that despite extensive mechanistic evidence supporting the role of lncRNAs across cancer hallmarks, important challenges remain regarding functional heterogeneity, clinical validation, and translational implementation. Therefore, computational and AI-based methods have been explored for multi-omics integration in precision oncology [66, 67].

4. ARTIFICIAL INTELLIGENCE IN LNCRNA RESEARCH

lncRNAs are pivotal regulators of gene expression, development, and disease. However, their functional characterization remains challenging due to their vast numbers, structural complexity, and lack of protein-coding potential. Deep-learning approaches have been applied to

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Table 1. Representative lncRNA-associated mechanisms in cancer hallmarks and therapeutic resistance, with experimental models and evidence categories.

lncRNA	Cancer setting	Reported mechanism or effect	Hallmark/response	Experimental model	Evidence	Source
MALAT1	Hypoxic TNBC	Regulation of WTAP protein and hypoxia-associated EMT responses	Migration/EMT	MDA-MB-468 and MDA-MB-231 cells	I	[18]
MEG3	Prostate cancer	Reduced Cyclin D1 and Bcl-2; increased Bax and caspase-3 activation	Growth arrest/apoptosis	PC3 and DU145 cells; PC3 xenografts; paired patient tissues	I + V + H	[23]
FEZF1-AS1	Colorectal cancer	PCK2-associated protein regulation; partial rescue by PCK2 re-expression	Proliferation	HCT-116/SW480 cells; mouse xenografts; tissue and TCGA analyses	I + V + H	[27]
GAS5	Gastric cancer	miR-106a-5p-associated inhibition of Akt/mTOR signalling	Growth/apoptosis	GC cell lines; mouse xenografts; patient tissues	I + V + H	[29]
FAM83H-AS1	Colorectal cancer	Notch-associated proliferation; pathway rescue experiments	Proliferation	SW480/HT29 cells; patient tissues	I + H	[28]
GAS5	Lung adenocarcinoma	Reduced IGF-1R expression and enhanced gefitinib-induced cell death	Drug response/apoptosis	A549 cells; mouse xenografts; patient tissues	I + V + H	[33]
NKILA	HCC	Suppression of NF-κB/Slug-associated EMT	Invasion/metastasis	SMMC-7721/HCC-LM3 cells; tail-vein mouse model; patient tissues	I + V + H	[34]
H19	Colorectal cancer	miR-194-5p/SIRT1-associated autophagy	5-FU resistance	CRC cell models; patient tissues	I + H	[38]
TUSC7	ESCC	miR-224/DESC1-associated regulation of drug resistance	Cisplatin response	ESCC cells; KYSE30 xenografts; patient cohort	I + V + H	[36]
LINC00969	EGFR-mutant NSCLC	EZH2-mediated promoter repression and METTL3-mediated NLRP3 RNA modification	Gefitinib resistance/pyroptosis	PC9/GR and HCC827/GR cells; mouse xenografts; patient tissues	I + V + H	[41]
TERRA	HCC	TRF/TERRA-associated regulation of telomerase activity and telomere length	Telomere maintenance	SNU-739/SNU-368 cells; mouse models; paired HCC tissues	I + V + H	[60]
TERRA	ALT-positive models	METTL3/m6A/hnRNPA2B1-associated telomeric R-loop formation	Telomere maintenance	U2OS and ALT-positive neuroblastoma cells; neuroblastoma xenografts	I + V	[61]

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MEG3	Ovarian cancer endothelium	miR-376a/YBX1/RASA1-associated suppression of tube formation	Angiogenesis	Primary tumor-derived endothelial cells; public patient datasets	I + H	[15]
MEG3	Glioblastoma	FUBP3-dependent VGF expression promotes angiogenesis	Angiogenesis	T387/T4121 GSCs; endothelial conditioned-medium assays; orthotopic mice; human datasets	I + V + H	[16]
HULC	HCC	miR-107/E2F1/SPHK1-associated angiogenesis	Angiogenesis	Hepatoma cells/HUVECs; chick CAM; mouse xenografts; HCC tissues	I + V + H	[48]
XIST	Glioma-associated endothelium	miR-137/FOXC1/CXCR7-associated endothelial responses	Angiogenesis/BTB function	hCMEC/D3 cells co-cultured with glioma cells	I	[49]
HOTAIR	Breast cancer	PRC2 redistribution and H3K27 trimethylation	Invasion/metastasis	Breast cancer cells; mouse models; human tumor analyses	I + V + H	[52]
UCA1	Gastric cancer	miR-203/ZEB2-associated invasive phenotype	Invasion/metastasis	BGC-823/SGC-7901 cells; tail-vein mouse model; patient tissues/TCGA	I + V + H	[53]
ANCR	Breast cancer/EMT models	Reduced RUNX2 expression and attenuation of TGF-β-associated EMT	EMT/metastasis	MCF10A/MDA-MB-231 systems; mouse lung-colonization model; paired tissues	I + V + H	[54]

Evidence abbreviations: I, in vitro evidence from cultured cancer cells or primary cells; **V,** in vivo or preclinical evidence from animal models; **H,** human-associated evidence based on patient tissues, blood samples, or observational cohorts. The presence of H indicates an observational human association and does not establish a molecular mechanism in patients or clinical efficacy of an lncRNA-directed intervention. None of the studies listed in the table provides clinical validation of an lncRNA-targeted treatment.

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the prediction and annotation of lncRNA-mediated mechanisms [65].

Advances in deep learning architectures, including convolutional neural networks (CNNs), recurrent neural networks (RNNs), and attention-based models, have enhanced the extraction of intricate sequence patterns and contextual features from genomic data. Candidate interactions with DNA, RNA, and proteins can be predicted by these models. Their regulatory roles require experimental confirmation [65]. Several specialized AI-based tools and computational frameworks have been developed for lncRNA analysis. LncADeep is a deep-learning tool for lncRNA identification and functional annotation. Its functional annotations are inferred computationally, including from predicted interacting proteins, and should be distinguished from experimentally established functions [68]. Graph-based methods such as GCNLDA and GCRFLDA have also been proposed for lncRNA–disease association prediction [69, 70].

GCNFORMER combines graph convolution with a transformer encoder to predict lncRNA–disease associations using lncRNA, miRNA, and disease information. Its evaluated output is an association score, rather than an experimentally established molecular structure or mechanism [71].

AI-based methods have been developed for RNA structure and interaction prediction. Their performance remains dependent on available structural data and the RNA classes evaluated [72]. Deep-learning classifiers have been developed to distinguish lncRNAs from protein-coding transcripts. Performance was evaluated on the datasets used in each study and should not be interpreted as experimental functional annotation [73]. Disease-association prediction should be distinguished from patient-level prognosis and treatment-response modelling. For example, GCNFORMER was evaluated using curated association data and computational case studies. These analyses can prioritize candidates for investigation, while clinical prediction requires separate evaluation in appropriately defined patient cohorts [71].

Recent graph-based models provide examples of association prediction under defined computational benchmarks. HGCMLDA used hypergraph contrastive learning and multiscale feature fusion and evaluated held-out associations from curated datasets. Its independent test set was drawn from the same association collection, rather than an external clinical cohort. Such results support benchmark-specific predictive performance, while generalization to new biological settings and clinical use requires separate validation [74].

5. LIMITATIONS AND CHALLENGES OF AI-BASED LNCRNA ANALYSIS

AI-based lncRNA analysis is affected by incomplete annotation. Low expression and tissue specificity can limit transcript detection, and greater inter-individual expression variability has been reported for lncRNAs than for protein-coding genes [8, 9]. Tissue and donor representation should therefore be considered when expression-based models are developed. Annotation is also revised as additional transcripts and biological contexts are incorporated. In LncBook 2.0, the structures of 21,305 lncRNA genes were updated, illustrating the effect of annotation version on transcript-level analyses [75]. Expression-based analyses can also be distorted by batch effects. Technical features may be associated with the outcome of interest and may be mistaken for biological signals. Missing measurements, unpaired samples, and differences between data modalities further complicate multi-omics integration[76, 77]. Sparse expression and incomplete annotation create additional challenges in single-cell and spatial transcriptomic datasets [78]. These limitations should be considered when low-abundance lncRNAs are analysed across heterogeneous datasets.

Experimental evidence is also uneven. LncRNADisease v3.0 records different evidence types and distinguishes general associations from relationships supported by gain- or loss-of-function experiments [79]. EVLncRNAs 3.0 specifically curates functional lncRNAs supported by low-throughput experimental studies [80]. Expression associations and perturbation-supported functions should therefore be distinguished when training labels are assembled.

Finally, mechanistic interpretation may be limited by complex model architectures. Limited interpretability and reduced robustness on unseen data have been identified as concerns in single-cell and spatial transcriptomic analyses [78] . For lncRNA applications, performance should be evaluated in independently collected biological datasets before generalizability is claimed. Computational accuracy should not be treated as evidence of a validated molecular mechanism.

6. CONCLUSION

This review summarizes evidence that lncRNAs contribute to the regulation of proliferation, cell-death responses, telomere maintenance, angiogenesis, and metastatic phenotypes. Their effects depend on the cellular and molecular setting, and findings from experimental models should be distinguished from human associations and clinical validation. Selected lncRNAs remain candidates for biomarker development and therapeutic investigation, but their clinical relevance requires further evaluation. AI methods can support computational identification, annotation, and prioritization of candidate disease associations. Progress will depend on reliable annotations, appropriate model evaluation, functional confirmation, and validation in independently collected patient cohorts.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethical statement

This study is a review article based on previously published literature. No new data involving human participants or animals were collected; therefore, ethical approval was not necessary.

Declaration of AI-assisted technologies

During the preparation and revision of this manuscript, ChatGPT (OpenAI) and Claude (Anthropic) were used to assist with grammar and readability. Claude was also used to assist with the preliminary visual layout of Fig. 1. The scientific content of the figure was determined and verified by the authors, who prepared the final figure. All content was reviewed and verified by the authors, who take full responsibility for the scientific integrity of the manuscript.

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