Section 1

Biochemistry of Long Non-Coding RNAs

Chapter 1

Perspective Chapter: Decoding Cancer's Silent Players – A Comprehensive Guide to LncRNAs

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Abstract

Long non-coding RNAs (LncRNAs) are RNAs that do not code for proteins and were thus earlier known as Junk RNAs. Recently, LncRNAs have emerged as critical regulators in the expression of coding genes and various important biological signaling pathways, thus controlling crucial biological and developmental processes. Reports of LncRNAs association with several diseases including cancer have also been implicated. LncRNAs play a crucial diverse role in regulating cancer pathways, thus influencing tumorigenesis, progression, and metastasis. They can function both as oncogenes or tumor suppressors, modulating key signaling pathways and cellular processes. Mutation or epigenetic-induced aberrant expression of LncRNAs dysregulates different essential biological pathways, leading to malignant phenotype and cancer hallmarks in different types of cancer. Tumor cells secrete specific endogenous LncRNAs into biological fluids depending on the cancer type, giving rise to stable circulating LncRNAs, thus proving to be of great potential as non-invasive or minimally invasive diagnostic biomarkers. In this chapter, we explore the multifaceted roles of LncRNAs in various cancer types, highlighting their potential as diagnostic/prognostic biomarkers and therapeutic targets. Additionally, we discuss innovative strategies for targeting LncRNAs in cancer treatment, including RNA interference and CRISPR technology. This chapter will provide a comprehensive overview of LncRNAs' implications in cancer research and personalized medicine.

Keywords: long non-coding RNAs, cancer, mechanisms, biomarkers, prognosis, therapeutic target, personalized medicine

1. Introduction

With the advent and development of advanced high-throughput sequencing technologies such as microarray and RNAseq, besides coding genes, many non-coding RNAs that do not code for proteins were identified. The most distinguished non-coding RNAs are microRNAs (miRNAs) and long non-coding RNAs (LncRNAs). LncRNAs are transcripts that are greater than 200 nucleotides in length and have no long open reading frames (>100 amino acids), regulating gene expression of target

genes at transcriptional, post-transcriptional, translational, and epigenetic levels by acting as guides, scaffolds, decoys, or signals [1–5]. LncRNAs play vital roles in important biological and developmental processes, such as genomic imprinting, X-chromosome inactivation, chromatin modification, and alternative splicing, as well as affecting various cellular activities, such as proliferation, differentiation, and survival [1, 6]. Due to their multifaceted and diverse functions, LncRNAs have been implicated in a large number of human diseases including coronary disorders, type 2 diabetes, neurological disorders, and various types of cancer [6]. Other than cardiovascular disorders, cancer is thought to be the leading cause of mortality worldwide [7]. Increasing evidence of LncRNAs association with cancer has been found in the literature [1, 8]. LncRNAs play a crucial role in regulating cancer pathways, thus influencing tumorigenesis, progression, and metastasis [1]. Literature suggests that altered expression of LncRNAs in tumors is closely linked to the manifestation of cancer hallmarks such as unregulated proliferative signaling, avoiding growth suppressors, preventing cell death (apoptosis), uncontrolled replication, triggering angiogenesis, initiating invasion and metastasis, aberrant metabolic pathways, immune evasion, genomic instability, and inflammation [5]. Although the mechanisms are poorly understood, LncRNAs play a pivotal role in tumorigenesis and progression by regulating gene expression and fine-tuning signaling pathways [1, 9]. Several LncRNAs, such as MALAT1, PCA3, HOTAIR, ANRIL, and MEG3, have been reported to be upregulated or downregulated in a variety of human cancers [8, 10–12]. Research indicates that LncRNAs, known for their high specificity and precision, hold potential as cancer biomarkers [12, 13]. Their unique expression and diverse functions across cancer types make them promising for diagnosis, prognosis, and treatment. Additionally, LncRNAs can be collected noninvasively from body fluids, tissues, and cells, serving either as independent or supplementary biomarkers to enhance diagnostic and prognostic accuracy [13]. This chapter provides an overview of the roles of different LncRNAs in the development and progression of various cancer types, emphasizing their promise as diagnostic, prognostic markers, and therapeutic targets (**Figure 1**). It also covers novel approaches to targeting LncRNAs, such as RNA interference (RNAi) and CRISPR, offering a thorough overview of their impact on cancer research and personalized medicine.

2. LncRNAs in tumorigenesis and cancer progression

LncRNAs can function both as oncogenes or tumor suppressors, regulating various aspects of cancer initiation and progression [14]. Abnormal expression of oncogenic and tumor-suppressive LncRNAs disrupts tumor suppressor gene activity by reducing their transcription and translation, while promoting the expression and translation of oncogenes. This imbalance drives processes such as cellular proliferation, differentiation obstruction, migration, invasion, metastasis, genomic instability, transformation into malignant type, tumor initiation and progression, and resistance to chemotherapy and radiotherapy [10].

2.1 LncRNAs in tumorigenesis

Several LncRNAs have been reported to be overexpressed in a variety of human cancers, for example, MALAT1 [10, 15], HOTAIR [16, 17], ANRIL [18], etc., whereas several others are downregulated, for example, MEG3 [19], PANDA [20], PCAT29

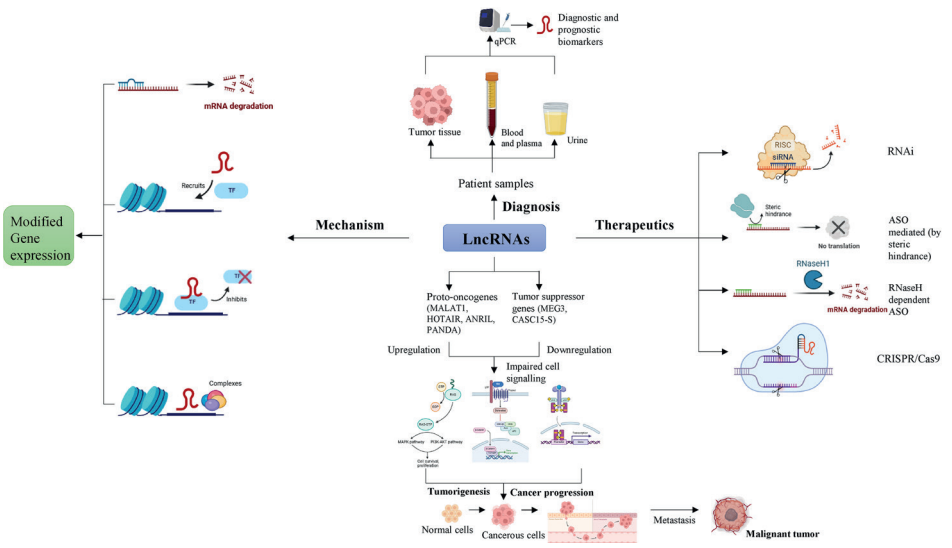

Figure 1.
Schematic representation of the influence of LncRNAs in cancer research, highlighting their role in tumorigenesis, cancer progression, diagnosis/prognosis and therapeutics.

[21], and CASC15-S [22]. Also, it has to be noted that the same LncRNA can either act as an oncogene or a tumor suppressor depending on the type of cancer; for example, MALAT1 was initially reported to be upregulated in human mantle cell lymphoma, renal cell carcinoma tissues, bladder cancer, pancreatic ductal adenocarcinoma tissues, human melanoma, ovarian cancer, lung cancer, and liver cancer [10]. On the other hand, two recent in-depth studies show that MALAT1 has tumor-suppressive effects in colorectal and breast cancers [10, 23]. Thus, demonstrating the cancer type-specific role of LncRNAs in cancer development.

MALAT1 (metastasis-associated in lung adenocarcinoma transcript 1) is one of the most researched LncRNAs in cancer because it is readily detectable and functionally investigated, and it is substantially expressed in cancer tissues [10]. Cancer tissues are thought to release MALAT1, an intergenic transcript found on human chromosome 11q13.1, into the bloodstream through exosomes since it is highly expressed in both serum and cancer tissues. As a result, its expression in blood is similar to that of the primary tumors [11]. MALAT1 was initially found to be significantly linked to non-small cell lung cancer (NSCLC) metastases [5]. Further research showed that, in contrast to normal cervical squamous cell samples, LncRNA-MALAT1 expression was elevated in cervical cancer cell lines [24]. Also, the laryngeal cancer cells' expression levels of LncRNA-MALAT1, miRNA-503-5p, and FOXK1 were investigated. The levels of miRNA-503-5p were low, while those of LncRNA-MALAT1 and FOXK1 were high. This implies that LncRNA-MALAT1 and miRNA-503-5p have a negative correlation and that miRNA-503-5p is one of its target regulatory genes [11]. Despite the fact that MALAT1 has been found to be overexpressed in the majority of human cancer tissues, its oncogenic or tumor-suppressive function in breast cancer remains up for debate [10]. MALAT1 has been found to be abnormally upregulated in human breast cancer tissues, and high expression levels of MALAT1 are associated with a poor prognosis for patients. By binding miRNA-1, miRNA-124, and miRNA-448, MALAT1 functions as a competitive endogenous RNA (ceRNA) to decrease CDC42 and increase CDK4

expression, which promotes invasion, migration, and cell cycle progression in breast cancer [10, 25]. However, recent comprehensive studies show that MALAT1 has tumor-suppressive effects in breast cancers. By binding and sequestering miRNA-17, miRNA-20a, and miRNA-106b, PTEN increases the expression of MALAT1, which in turn inhibits the migration and invasion of breast cancer cells by lowering integrin β4 (ITGB4) and the pro-metastatic Epithelial Cell Adhesion Molecule (EpCAM) [23].

LncRNA HOTAIR (HOX Transcript Antisense Intergenic RNA) dysregulation is also frequently found in several types of human cancer. Because it is overexpressed in many malignancies, HOTAIR can function as a pro-oncogene and be linked to a number of cancer hallmarks, including apoptosis inhibition, cellular proliferation, and genomic instability [5]. Overexpression of HOTAIR, an oncogene that is transcribed from the HOXC locus during normal development, can accelerate the development of gastric cancer [9]. Progesterone receptor (PGR), protocadherin 10 (PCDH10), protocadherin β5 (PCDHB5), and junctional adhesion molecule 2 (JAM2) are tumor suppressors that can be inhibited by overexpression of HOTAIR, hence increasing tumor growth [9, 26, 27]. The aberrant expression of LncRNA HOTAIR promotes the proliferation, cell cycle, and migration of gastric cancer cells, and it can suppress the expression of miRNA-217 and increase the resistance of gastric cancer cells to doxorubicin and paclitaxel [9, 28]. It has also been reported that prostate cancer (PCa) tissues and cells have high levels of HOTAIR expression which is linked to anti-apoptosis, migration, invasion, proliferation, and tumor formation [5]. LncRNA HOTAIR has also been reported to be upregulated in breast carcinoma, colorectal cancer (CRC), hepatocellular carcinoma (HCC), laryngeal squamous cell carcinoma (LSCC) tissues [5]. Peng et al. [29] in their study have shown that HOTAIR downregulates miRNA-34a to promote the development of colon cancer.

MEG3 (Maternally Expressed 3), a tumor suppressor on chromosome 14q32.2, is typically downregulated in cancer cells. In bladder cancer, MEG3 overexpression induces autophagy and promotes P53 accumulation [9]. In NSCLC, elevated Heterogeneous nuclear ribonucleoprotein A2B1 (HNRNPA2B1) expression correlates with distant metastasis, poor survival, and serves as an independent prognostic marker. HNRNPA2B1 knockdown *in vitro* and *in vivo* reduces cell proliferation and metastasis, while its overexpression has the opposite effect. Mechanistically, HNRNPA2B1 mediates m^6A modification of MEG3, and its inhibition leads to decreased MEG3 m^6A while increasing the mRNA levels. MEG3 functions as a miRNA-21-5p sponge to upregulate PTEN, inhibiting PI3K/AKT signaling and suppressing proliferation and invasion. Low MEG3 or high miRNA-21-5p expression predicts poor NSCLC survival, identifying the HNRNPA2B1/MEG3/miRNA-21-5p/PTEN axis as a potential therapeutic target [19].

LncRNA-TSLNC8 (Tumor Suppressor Long Non-Coding RNA on Chromosome 8p12) plays a critical role in various cancers, including glioma, liver, lung, breast, melanoma, and gastric cancers [30]. Acting as a tumor suppressor, TSLNC8 inhibits tumor progression and reduces chemoresistance when overexpressed. It functions as a ceRNA, sequestering specific microRNAs, and is involved in multiple signaling pathways implicated in cancer development and progression [30].

The oncofetal LncRNA H19, typically repressed postnatally, is re-expressed in various cancers, including HCC and rectal cancer [31]. Although not a classical oncogene, H19 was the first LncRNA identified as overexpressed in HCC. It influences cancer progression through pathways such as acting as a precursor to miRNA-675, whose increase promotes tumor growth, or functioning as a ceRNA that sponges miRNAs like let-7, reducing tumor suppressor activity and encouraging proliferation [9, 31]. Cancer susceptibility candidate

9 (CASC9) is a LncRNA overexpressed in oral SCC and HCC. It binds to hnRNP L to form a complex that regulates HCC cell viability by modulating the PI3K/AKT signaling pathway [32]. Small nucleolar RNA host gene 1 (SNHG1), located on chromosome 11q12.3, hosts eight small nucleolar RNAs (snoRNAs), which is another LncRNA overexpressed in various cancers [33]. In HCC, LncRNA SNHG1 levels are elevated in tissues and cell lines compared to normal counterparts. It promotes HCC progression by sponging miRNA-195, increasing AEG-1 protein expression [33, 34]. SNHG1 is also significantly upregulated in breast cancer, esophageal squamous cell carcinoma, PCa, NSCLC, colon cancer, and bladder cancer [33].

Several other LncRNAs have been reported to be involved in cancer development and progression, which has been mentioned in **Table 1.**

LncRNA	Cancer type	Oncogenic or Tumor suppressor	Expression	Mechanism	Reference
MALAT1	Colorectal	Tumor suppressor	Down-regulated	Non-canonical PTEN miRNA- MALAT1 axis	[23]
	Breast	Tumor suppressor	Down-regulated	Non-canonical PTEN miRNA- MALAT1 axis	[23]
	Bladder	Oncogenic	Upregulated	TGF-β induced MALAT 1 upregulation resulting in EMT	[15]
	Gallbladder	Oncogenic	Upregulated	Functions as a ceRNA to regulate miRNA-206	[35]
	Malignant Melanoma (Skin)	Oncogenic	Upregulated	Acting as a sponge for miRNA-22	[36]
PVT1	Lung	Oncogenic	Upregulated	Interacts with miRNAs and proteins	[37]
CASC9	HCC	Oncogenic	Upregulated	PI3K/AKT-signaling cascade	[32, 38]
PCAT29	Prostate	Tumor suppressor	Down-regulated	Directly regulated by the androgen receptor (AR), which binds to the promoter of PCAT29	[21]
loc285194	Colon	Tumor suppressor	Down-regulated	Reciprocal repression of loc285194 and miRNA-211 possibly via pathway involving RISC complex	[13]
DRAIC	Prostate	Tumor suppressor	Down-regulated	AR binds to the *DRAIC* locus and represses *DRAIC* expression	[39]
TUG1	Colorectal	Oncogenic	Up-regulated	SP1, an upstream transcription factor interacts with TUG1 and regulates the downstream miRNA-421/KDM2A/ERK axis	[40]

LncRNA	Cancer type	Oncogenic or Tumor suppressor	Expression	Mechanism	Reference
CCAT1	hepatocellular carcinoma	Oncogenic	Up-regulated	Acting as a let-7 sponge	[41]
	gallbladder cancer	Oncogenic	Up-regulated	Acting as a miRNA-218 sponge	[42]
GMDS-AS1	Colorectal	Oncogenic	Up-regulated	GMDS-AS1 targets HuR directly activating STAT3/Wnt signaling	[43]
MEG3	NSCLC	Tumor suppressor	Down-regulated	HNRNPA2B1-mediated m^6A modification of the LncRNA MEG3 facilitates tumor growth and metastasis by modulating the miRNA-21–5p/PTEN pathway.	[19]
PTTG3P	NSCLC	Oncogenic	Up-regulated	PTTG3P/ILF3/E2F1 axis	[44]
G077640	ESCC	Oncogenic	Up-regulated	Enhancing HIF1α stability and downstream glycolytic signaling pathway	[45]
GAS5	Cervical	Tumor suppressor	Down-regulated	siRNA-mediated knockdown of GAS5	[46]
HOTAIR	Pancreatic	Oncogenic	Up-regulated	Polycomb Repressive Complex 2 (PRC2) -dependent and -independent	[16]
	Gastric	Oncogenic	Up-regulated	Possibly via interaction with PRC2	[17]
ANRIL	NSCLC	Oncogenic	Up-regulated	Possibly by regulating (silencing) KLF2 and P21 transcription	[18]
TP73-AS1	Ovarian	Oncogenic	Up-regulated	Modulation of MMP2 and MMP9	[47]

Table 1.
List of some LncRNAs reported to be involved in cancer development and progression.

2.2 LncRNAs and metastasis

Metastasis, the spread of cancer to distant sites, is a leading cause of cancer-related deaths. It involves steps like epithelial–mesenchymal transition (EMT), migration, anoikis resistance, and angiogenesis [48, 49]. LncRNAs play a key role in promoting metastasis by driving EMT [5], angiogenesis, invasion, migration [32, 50, 51], organ-specific colonization, apoptosis evasion [37], and shaping the metastatic tumor microenvironment [49]. They directly regulate metastasis *in vitro* and *in vivo* across various cancers [48].

LncRNA MALAT1 was initially linked to NSCLC metastasis. Its overexpression promotes brain metastasis in NSCLC by driving EMT and enhances tumor proliferation and metastasis in osteosarcoma through the PI3K/Akt pathway [5]. MALAT1 also regulates EMT *via* this pathway in osteosarcoma progression and influences HCC through the mTOR pathway [5, 52, 53]. In ESCC, MALAT1 upregulation promotes proliferation and metastasis by dephosphorylation of the ATM-CHK2 pathway, while in gastric cancer, it accelerates tumor growth and spread [54, 55]. Clinical studies identify MALAT1 overexpression as a poor prognostic marker in pancreatic cancer [5]. In breast cancer, MALAT1 enhances angiogenesis, potentially *via* miRNA-145 regulation [56]. MALAT1's role in cancer metastasis is primarily mediated through EMT [48].

Hou et al. [57] found that LncRNA-ROR is upregulated in breast tumor tissues, promoting EMT by acting as a ceRNA for miRNA-205 in mammary epithelial cells. In triple-negative breast cancer (TNBC), ROR serves as a ceRNA sponge for miRNA-145, affecting its target ARF6, a key regulator of tumor cell invasion and metastasis. ARF6 influences E-cadherin localization and cell–cell adhesion. These findings highlight the LncRNA-ROR/miRNA-145/ARF6 pathway in regulating TNBC metastasis [48, 58]. LncRNA-TTN-AS1, an oncogene overexpressed in ESCC tissues and cell lines, promotes proliferation and metastasis. It enhances Snail1 expression by sponging miRNA-133b, triggering the EMT cascade. Additionally, LncRNA-TTN-AS1 upregulates FSCN1 expression through miRNA-133b sponging and HuR upregulation, driving ESCC invasion. miRNA-133b directly regulates FSCN1, a key protein linked to ESCC metastasis [59]. Another LncRNA SNHG1, highly upregulated in PCa and sublocalized in the nucleus, promotes PCa metastasis by activating the EMT pathway [33]. Tan et al. [60] found that SNHG1 competitively interacts with hnRNPL, disrupting CDH1 translation through the hnRNPL-CDH1 axis, thereby triggering EMT and tumor spread. LncRNA LOXL1-AS1 upregulation is linked to increased proliferation, migration, metastasis, and EMT while suppressing apoptosis in various cancers, including ovarian, cervical, endometrial, gastric, CRC, esophageal, lung, laryngeal, liver, breast, and PCa [61]. Low GAS5 expression is associated with increased apoptosis in TNBC and ER-positive breast cancer, correlating with lymph node metastasis, advanced clinical stage, and poor survival [5, 62]. In CRC, reduced GAS5 levels are linked to tumor size, advanced TNM stage, lymph node metastasis, low histological grade, poor survival, distant metastasis, and higher recurrence rates [5]. However, overexpression of GAS5 has been linked to early-stage CRC liver metastases [63]. PCAT-1 upregulation is strongly linked to TNM stage and metastasis in HCC and osteosarcoma, as well as tumor invasion and lymph node metastasis in gastric and esophageal cancers [5]. Zhang et al. [64] revealed that PCAT-1 acts as a ceRNA against miRNA-122, and PCAT-1 silencing reduced Wnt/b-catenin signaling *via* miRNA-122 suppression and WNT1 expression, which in turn prevented the advancement of ESCC. The overexpression of HOTAIR was found to be associated with tumor growth, metastasis, migration, cell proliferation, invasion, TNM stage, decreased survival, and a poor prognosis for patients with CRC as compared to healthy controls [5].

2.3 LncRNAs' interaction with signaling pathways

Abnormal signal transduction is a key driver of tumorigenesis and cancer progression, with LncRNAs acting as critical regulators by modulating various signaling pathways [1]. Several key signaling pathways regulated by LncRNA to promote cancer development and progression have been discussed in brief below.

Wnt/β-catenin pathway: The Wnt/β-catenin pathway is often dysregulated in tumorigenesis, influencing proliferation, invasion, metastasis, and apoptosis. LncRNAs regulate this pathway, acting as tumor suppressors or promoters [1]. For example, HOTAIR promotes breast cancer invasion and metastasis by activating the Wnt/β-catenin pathway [65].

STAT3 signaling pathway: The STAT3 signaling pathway, particularly JAK/STAT, is a key oncogenic driver in various cancers. For example, some miRNAs and LncRNAs act as STAT3 negative regulators, binding to its mRNA or modulating its expression to inhibit CRC progression. Conversely, certain LncRNAs, like HOTAIR, promote CRC development by enhancing STAT3 activity, functioning as oncogenes [66].

MAPK pathway: The MAPK pathway is involved in regulating cell proliferation, differentiation, transformation, and apoptosis, contributing to inflammation and tumor development by phosphorylating key cellular components [67]. Many LncRNAs modulate this pathway. For instance, LncRNA XIST targets miRNA-194-5p, reducing its expression and regulating MAPK1, while its silencing inhibits hepatoma cell proliferation and invasion [67]. Similarly, MALAT1 knockdown suppresses MEK/ERK/MAPK/JNK phosphorylation leading to inhibition of ERK/MAPK pathway, reducing gallbladder carcinoma metastasis and invasiveness [68].

PI3K/AKT signaling pathway: The PI3K/AKT signaling pathway is associated with the regulation of cell proliferation, survival, and migration and is abnormally activated in cancers like breast, colorectal, ovarian, pancreatic, and endometrial cancer [50]. Interaction of phosphatidylinositol-3,4,5-trisphosphate (PIP3) and pleckstrin homology (PH) domain drives AKT phosphorylation at Ser473 and Thr308 by PDK1 and mTOR resulting in AKT activation, which then regulates tumor growth and metastasis [50, 69, 70]. LINK-A enhances interactions between PtdIns(3,4,5)P3 and the AKT PH domain, driving AKT hyperphosphorylation, resistance to AKT inhibitors, and promoting tumorigenesis and metastasis [71].

Notch signaling pathway: The Notch signaling pathway regulates cell differentiation, proliferation, and apoptosis, playing diverse roles in tumorigenesis and progression by influencing genes like MYC, cyclin-D1, and p21 [1, 72]. LncRNA LINC01152 acts as an oncogene in glioblastoma multiforme by activating Notch signaling through miRNA-466 interaction and upregulating MAML2, a transcriptional co-activator 2, thereby promoting tumor progression [73].

TGF-β signaling pathway: The TGF-β signaling pathway maintains homeostasis in normal tissues, regulating cell proliferation, motility, and differentiation. However, in tumors, it promotes malignancy. LncRNAs significantly influence TGF-β pathway activity, impacting cancer progression [1]. For instance, downregulation of LncRNA-ANCR promotes breast cancer metastasis *via* association with TGF-β signaling pathway [74].

Unsurprisingly, multiple signaling pathways may be regulated by a single LncRNA. MALAT1 acts as an oncogene by activating the Wnt/β-catenin pathway *via* β-catenin upregulation and GSK3β downregulation. It also activates the Notch signaling pathway by increasing JAG1 (Jagged1) expression through miRNA-124 inhibition [1, 75]. Additionally, LncRNAs can link multiple pathways; for example, BCAR4 in breast cancer connects the Hippo and HH pathways. Hippo effector YAP promotes BCAR4 expression, activating HH signaling to drive glycolysis by upregulating HK2 and PFKFB3, reprogramming glucose metabolism [1, 76].

3. Diagnostic and prognostic potential

Cancer's high mortality rate is partly attributed to inadequate early detection methods and unreliable diagnostic tools like certain protein biomarkers. Most current biomarkers are protein-based, such as glycoproteins, detected through tissue biopsy and immunohistochemistry (IHC) to identify cancer subtypes. However, protein markers often produce false-positive or false-negative results. Conventional serological markers like CA153, CA125, CA27.29, and CEA are also criticized for low specificity and sensitivity. These limitations arise from antibody-based detection, where antibodies may lack specificity or cross-react with other tissues. Furthermore, traditional histology relies on invasive biopsies, discouraging some patients from undergoing diagnostics [77]. Therefore, non-invasive, non-protein biomarkers are urgently needed. Liquid biopsy enables early cancer detection through minimally invasive, serial testing of body fluids, allowing real-time tumor progression monitoring [78]. LncRNAs, detectable in blood, plasma, serum, and urine *via* real-time PCR, are stable in circulation and resistant to nuclease degradation. Their abundance and accessibility make circulating LncRNAs highly promising diagnostic biomarkers [78, 79]. Several LncRNAs, including PCA3, HOTAIR, HULC, MALAT1, and H19, are promising minimally invasive diagnostic and prognostic cancer biomarkers found in body fluids (**Table 2**). Some of these LncRNAs have already been proven effective for diagnostic and prognostic use in clinical settings [12, 79]. PCA3 has been approved by the US FDA as a urine biomarker for PCa, offering better sensitivity and specificity than the Prostate-Specific Antigen (PSA) blood test due to its higher expression in PCa patients [12]. It is more reliable than other circulating nucleic acids due to its high stability in the bloodstream and resistance to nuclease degradation [77]. Genome-wide studies have identified thousands of LncRNAs with differential expression between normal tissues and tumors, highlighting their potential as cancer-specific biomarkers. LncRNA expression profiles can also help identify cancer subtypes, providing insights into tumor behavior and prognosis [8]. MALAT1 is a promising diagnostic biomarker for lung cancer, detectable in blood, and is also elevated in the

LncRNA	Cancer type	Bioavailability	Prognosis	Reference
PCA3	Prostate	Urine	Poor prognosis	[80]
HOTAIR	OSCC	Saliva	Risk of metastasis	[81]
MALAT1	Lung	Blood	Increased risk of metastasis	[82]
H19	Gastric	Plasma, gastric juice	Poor prognosis	[83]
HULC	Pancreatic	Serum	Associated with tumor size, T staging, M staging, vascular invasion and overall survival	[84]
MEG3	Cervical	Tissue	Associated with tumor size, lymph node metastasis and overall survival	[85]
LncRNA-ATB	Breast	Serum	Associated with advanced TNM stage, large tumor size, high M stage and positive lymph node metastasis	[86]

Table 2.
List of some LncRNAs with potential diagnostic and prognostic value.

plasma and urine of PCa patients [12]. LncRNA HOTAIR, which is found to be highly expressed in the saliva samples of oral squamous cell carcinoma (OSCC) patients, is a strong candidate for diagnosing metastatic oral cancer, as its levels are higher in metastatic cases [12, 81].

Some LncRNAs are better suited as complementary biomarkers rather than standalone cancer diagnostic tools [12]. For instance, a five-LncRNA signature (AK001094, AK024171, AK093735, BC003519, and NR_003573) shows strong diagnostic and prognostic potential for gastric cancer (GC), with a combined AUC of 0.95 ± 0.025 in ROC curve analysis [87]. Similarly, three LncRNAs (lnc-MB21D1-3:5, lnc-PSCA-4:2, and lnc-ABCC5-2:1) were significantly dysregulated in GC and showed promising diagnostic performance with an AUC of 0.902 when combined [79]. For CRC, a panel of four LncRNAs (ZFAS1, SNHG11, LINC00909, and LINC00654) showed high diagnostic performance, particularly for early-stage disease, with an AUC of 0.937. Notably, SNHG11 showed the greatest potential for detecting precancerous lesions and early-stage tumors, indicating it could be a promising biomarker for CRC detection and a potential therapeutic target [88].

4. Therapeutic targeting of LncRNAs

LncRNAs have become promising pharmacological targets for treating complex malignancies due to their versatility in gene regulation and tissue-specific expression [89]. They offer advantages such as higher specificity and sensitivity, making them valuable for predicting therapeutic responses [90]. Unlike conventional treatments like chemotherapy, radiotherapy, and surgery, which often cause significant physical and mental stress and may lead to relapse, LncRNA-based approaches provide a more targeted and potentially effective alternative [91]. Furthermore, there is a growing need for personalized cancer therapy which relies on understanding genetic and molecular variations among patients that influence treatment responses [92]. A detailed analysis of LncRNA interactions with proteins, chromatin, and other RNAs can enable their use as precise biomarkers for diagnosis, prognosis, and targeted therapies in personalized medicine [93].

Abnormal levels of LncRNA in bodily fluids and tissues are consistent indicators of cancer and may be the focus of a potential treatment. Indeed, it has been demonstrated that cellular abnormalities linked to cancer can be successfully normalized by interfering with dysregulated LncRNA levels both *in vitro* and *in vivo* [91]. LncRNAs can be targeted through various approaches: (i) degrading pathogenic RNAs *via* siRNAs or chemically modified ASOs using dicer-, AGO-, or RNase H-dependent pathways; (ii) modulating LncRNA genes through promoter blockade or genome editing; and (iii) inhibiting RNA-protein interactions or formation of secondary structure by using ASOs or RNA-binding small molecules [94].

RNA interference (RNAi) is a well-established post-transcriptional gene silencing mechanism that is initiated by double-stranded RNA matching the target gene's sequence. It is a highly effective method for suppressing genes involved in specific biological or pathological processes by employing siRNAs that degrade mRNA during translation [95]. Traditional siRNA approaches have successfully targeted several LncRNAs, such as MALAT1, in human PCa cells, where they inhibited growth, invasion, and migration while inducing cell-cycle arrest [94, 96]. Similarly, siRNA-mediated knockdown of HOTAIR reduced matrix invasion in human breast cancer cells [27].

Another promising therapeutic tool for targeting LncRNAs is antisense oligonucleotides (ASOs), which interact with RNA through Watson–Crick base pairing. By binding to their target RNA, ASOs can modulate gene expression through mechanisms such as steric hindrance, splicing modification, or triggering RNA degradation [94]. In a luminal B breast cancer mouse model (MMTV–PyMT), subcutaneous delivery of MALAT 1-specific ASOs led to primary tumor differentiation and reduced metastasis by nearly 80% compared to nonspecific ASO controls. Additionally, ASOs targeting MALAT 1 decreased branching morphogenesis in 3D organoid models derived from MMTV–PyMT tumors and HER2-amplified mouse mammary tumors [97]. Beyond breast cancer, MALAT1-targeting ASOs have demonstrated strong antimetastatic effects in lung cancer xenograft models [94, 98].

Advances in genome editing technologies, such as CRISPR/Cas9, have enabled the transcriptional silencing of LncRNA-expressing genes through a technique known as CRISPR interference (CRISPRi). This method involves fusing a catalytically inactive Cas9 (dead-Cas9) with transcriptional repressors, which are guided to specific gene promoters by guide RNAs to inhibit transcription [94]. CRISPRi has been effectively utilized to selectively deactivate LncRNA genes across seven human cell lines, including six cancer types and one line of induced pluripotent stem cells (iPSCs) [99].

Nonetheless, there are several challenges associated with studying LncRNAs in the context of cancer. Many LncRNAs are expressed at low levels, raising concerns about their functional relevance in clinical oncology [100]. Differential expression patterns, alternative splicing, and tumor heterogeneity further complicate accurate analysis [101]. Techniques like RNAseq, single-cell RNAseq, and fluorescent RNA *in situ* hybridization (FISH) may address these issues but are time-consuming and resource-intensive [101, 102]. LncRNA-targeted therapies face delivery challenges, including poor membrane permeability of ASOs and siRNAs and difficulty targeting sub-nuclear LncRNAs [100, 101]. Additionally, toxicity and off-target effects remain significant hurdles, although bioinformatics and RNA-capture sequencing can help mitigate these problems. Functional validation of therapeutics *in vivo* is complicated by poor LncRNA conservation across species. Engineered models using larger human genomic segments or proteins may offer solutions. High-throughput methods and CRISPR-Cas9 technology could improve functional screening [101]. Profiling LncRNAs in body fluids or single cells is challenging due to low RNA abundance, fragmentation, and technical limitations in RNA sequencing. Advances like total RNA sequencing, RNA-capture sequencing, and specialized protocols such as SMART-seq are helping overcome these barriers [103]. Furthermore, conventional methods like RT-qPCR and microarray hybridization are time-consuming, while polyA-selection in RNAseq often misses non-polyadenylated LncRNAs [102, 103]. Emerging techniques, including total RNA sequencing, isothermal amplification and nanotechnology-based delivery systems, may improve clinical application feasibility [102, 103]. Addressing these challenges with innovative methods and technologies could unlock the full potential of LncRNAs in cancer diagnostics and therapeutics.

5. Conclusion and future perspectives

LncRNAs have been found to play a critical role in regulating cancer pathways and influencing tumorigenesis, progression, and metastasis. Aberrant expression of LncRNAs dysregulates essential biological pathways, leading to cancer hallmarks and malignant phenotype. Cancer-specific endogenous LncRNAs are secreted from

tumor cells into biological fluids, giving rise to stable circulating LncRNAs, thus proving to be of great potential as minimally invasive diagnostic and prognostic biomarkers. Also, LncRNAs have emerged as promising pharmacological targets for treating different types of cancer due to their higher specificity and sensitivity, diverse functional role in gene regulation, and tissue-specific expression. However, there are various challenges that are encountered while studying LncRNAs in the context of cancer such as low and differential expression patterns, off-target effects, profiling in single cells, delivery challenges, and technical limitations. Emerging techniques such as total RNA sequencing, isothermal amplification, and nanotechnology-based delivery systems, may help in addressing these challenges so that the full potential of LncRNAs in cancer diagnostics and therapeutics can be unlocked. Nanotechnology-based delivery systems, such as lipid or polymer nanoparticles carrying ASOs or siRNAs, represent a promising avenue for targeting oncogenic LncRNAs in cancers like TNBC [89, 100]. Furthermore, LncRNAs show significant promise for personalized medicine, particularly when combined with coding genes and SNPs. This approach could soon bring precision treatments closer to clinical application, especially for complex diseases like cancer, where there are genomic, epigenomic, and transcriptomic variations [93, 104].

The advancement of LncRNA applications in the future depends on technology that can recognize and validate their functions, structures, and mechanisms. Attempts to annotate LncRNAs like the formation of GENCODE and databases such as LncRNAtor, LNCipedia, and NONCODE are rapidly expanding knowledge of LncRNA loci [93]. Cutting-edge methodologies, including genome-wide DNA binding analysis such as ChiRP, CHART, RAP, and RNA-protein interaction mapping such as CLIP-seq and PAR-CLIP-seq [92], are paving the way for functional insights. Altogether, it can be concluded that there exists a multifaceted role of LncRNAs in various cancer types, highlighting their potential as diagnostic, prognostic biomarkers and therapeutic targets. Additionally, innovative strategies like RNAi and CRISPR technology may help in improving LncRNA-based cancer therapies as well as refine targeted approaches in personalized medicine.

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Conflict of interest

The authors declare no conflict of interest.

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