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The role of long noncoding RNAs in cancer: the dark matter matters

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Abstract

Sequencing technology has facilitated a new era of cancer research, especially in cancer genomics. Using next-generation sequencing, thousands of long noncoding RNAs (lncRNAs) have been identified as abnormally altered in the cancer genome or differentially expressed in tumor tissues. These lncRNAs are associated with imbalanced gene regulation and aberrant biological processes that contribute to malignant transformation. The functions and therapeutic potential of cancer-related lncRNAs have attracted considerable interest in the past few years. Although few lncRNAs have been well-characterized, researchers have recently made impressive progress in understanding lncRNAs and their novel functions, such as regulation of gene expression, metabolism and DNA repair. These latest findings reinforce the crucial roles of lncRNAs in cancer initiation and development, as well as their possible clinical applications.

Graphical abstract

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Conflict of interest

The authors declare no conflict of interest.

Introduction

The human genome contains thousands of noncoding regions, which were considered “junk DNA” for decades because of a lack of evidence for their transcription and failure to encode proteins. Recent technological advances, like tiling arrays and next-generation sequencing, revealed that the human genome, including the noncoding regions, is pervasively transcribed. Up to 75% of the human genome can be transcribed into RNAs, whereas less than 2% encodes proteins [1]. Much of the human transcriptome is composed of noncoding RNAs, including long noncoding RNAs (lncRNAs), one of the major subtypes. RNA transcripts >200 nucleotides without apparent protein-coding potential are considered lncRNAs. After the initial cloning of lncRNA genes such as *H19* and *Xist* from cDNA libraries, a large number of lncRNA genes have been identified genome-wide [2,3]. According to the latest GENCODE consortium release (version 26), 15,787 lncRNA genes have been identified in the human genome, yielding 27,720 lncRNA transcripts. Although lncRNAs are widely expressed in human tissues, they are under weaker selective constraints during evolution, and are less abundant and more tissue-specific than protein-coding genes [4].

Once known as genomic “dark matter,” current evidence indicates that lncRNAs participate in several biological processes (Figure 1). Acting as transcription signal activators, decoys, guides, or scaffolds for their binding partners are typical molecular mechanisms of lncRNAs [5]. They can regulate transcriptional activity in a *cis* or *trans* manner, by recruiting transcription factors or epigenetic modification complexes [6]. lncRNAs are also important for posttranscriptional regulation. They can modulate alternative splicing [7], undergo processing to small RNAs [8], regulate mRNA degradation and translation [9,10], or act as microRNA sponges (competitive endogenous RNAs) [11]. Moreover, a special subset of lncRNAs, enhancer RNAs, are transcribed from enhancer region or a gene neighboring locus and influence gene transcription [12]. In addition to their physiologic roles, lncRNAs are associated with diseases especially with cancer. For example, *HOTAIR* [13], *PCAT1* [14], *MALAT1* [15] and *FAL1* [16] have been implicated in a variety of human cancers.

Despite the large number of lncRNAs in the human genome, few have been well-characterized. The majority of lncRNA genes, especially cancer-related lncRNAs, need to be annotated and further explored. Here, we review recent research into the roles of lncRNAs in

cancer (Table 1), and provide an overview of newly annotated lncRNAs and their potential in cancer diagnosis and therapy.

LncRNAs in the cancer genome

Cancer is primarily a genetic disease involving multiple alternations in the genome, including copy number changes, somatic or germline variations, and changes in epigenetic modifications. Such alterations occur not only in protein-coding genes, but also in noncoding regions [17]. They may cause dysregulation of some lncRNA genes, which contributes to tumorigenesis, making them candidate cancer genes. A comprehensive study analyzing lncRNA alterations in 5,860 tumor samples from 13 cancer types from the Cancer Genome Atlas project revealed somatic copy number alterations (SCNAs) of lncRNAs in cancer [18]. On average, 13.16% and 13.53% of lncRNA genes have high-frequency gains and losses, respectively. Ovarian and lung squamous cell carcinomas have the most lncRNAs with high-frequency SCNAs. In addition to the genome-wide landscape, individual lncRNAs with copy number changes have also been identified and characterized. In melanoma, focal amplifications are observed at chromosome 3p13 and 3p14. At this locus, lncRNA *SAMMSON* is consistently co-gained with the melanoma-specific oncogene *MITF*, but the expression of *SAMMSON* is controlled by the lineage-specific transcription factor SOX10, instead of MITF. *SAMMSON* controls mitochondrial function and is critical for melanoma growth and survival; knockdown of *SAMMSON* dramatically decreases melanoma cell viability, regardless of *BRAF*, *NRAS*, or *TP53* mutational status [19]. *CCAT2*, which resides in the 8q24 amplicon and harbors a single nucleotide polymorphism (SNP), can modulate energy metabolism in colon cancer cells in an allele-specific manner [20].

Since approximately 80% of disease-associated SNPs are located in noncoding regions [21], overlap between lncRNAs and cancer-associated SNPs is common [18,22]. *NBAT-1*, an lncRNA that contains a high-risk neuroblastoma-associated SNP in its intron, controls cell proliferation and invasion, and predicts the clinical outcome of neuroblastoma. This SNP contributes to the differential expression of *NBAT-1* in neuroblastoma [23]. Notably, the potential tumor suppressor lncRNA *LINC00673*, the germline variation of which is associated with pancreatic cancer risk, inhibits pancreatic cancer cell proliferation by promoting PTPN11 degradation in an allele-specific manner. The germline variation of *LINC00673* creates a binding site for miR-1231, which diminishes *LINC00673* activity and confers susceptibility to tumorigenesis [24]. Germline variations can also affect lncRNAs by modulating their distal regulatory elements. A prostate cancer risk-associated SNP located in a distal enhancer of lncRNA *PCAT1* increases the binding of transcription factors ONECUT2 and AR to the enhancer and the *PCAT1* promoter, thereby upregulating *PCAT1* expression. *PCAT1* then recruits AR and LSD1 to the enhancers of *GNMT* and *DHCR24*, two genes implicated in prostate cancer development and progression [25].

In addition to SCNAs and genetic variation, the DNA methylation patterns in the promoter regions of lncRNAs are also distinct in tumor and normal samples, suggesting that DNA methylation-mediated epigenetic alterations occur at lncRNA gene promoter regions during tumorigenesis [18]. Evidence of copy number and methylation pattern changes supports the finding that lncRNAs are differentially expressed in many cancer types. Another large-scale

study analyzed lncRNA expression using data from 7,256 RNA-seq from tumors, normal tissues, and tumor cell lines [22]. This approach identified approximately 8,000 lineage- or cancer-associated lncRNAs, providing resources for future cancer biomarker identification.

Although the consequences of somatic mutations at noncoding regions are not well understood, growing evidence suggests that they may play an important role in human cancer. A genome-wide landscape of mutations in noncoding regions has been reported in chronic lymphocytic leukemia [26] and liver cancer patients [27]. Six lncRNA genes, including *NEAT1* and *MALAT1*, are recurrently mutated in liver cancer [27]. The efforts of the Pan-Cancer Analysis of Whole Genomes project, which aims to identify mutations in more than 2,800 cancer whole genomes, will help us further understand the roles of mutations in noncoding elements.

Annotation and characterization of lncRNAs in cancer

Although our knowledge about lncRNAs expands rapidly, the identification and characterization of functional lncRNAs in cancer remains challenging. Researchers are trying to annotate more functional lncRNAs by integrating computational and experimental approaches. Using a CRISPR–Cas9 single guide RNA library that targets regions involved in melanoma drug resistance, researchers have identified functional noncoding elements that contribute to gene regulation and chemotherapeutic resistance [28]. Similarly, a CRISPR–Cas9 paired guide RNA library has been applied to generate lncRNA deletions and perform “loss-of-function” screenings [29]. This high-throughput CRISPR-based approach identified 51 lncRNAs, 9 of which have been functionally validated, that positively or negatively regulate human cancer cell growth. Cancer type-specific lncRNAs associated with particular functions have also been identified. By combining global run-on sequencing and RNA-seq data from ER-treated MCF7 cells, researchers identified lncRNAs that regulate cell cycle gene expression and proliferation in breast cancer cells [30].

In addition to modulating gene regulation, lncRNAs are themselves subjected to regulation, directly or indirectly, by important cancer genes, such as *TP53* and *MYC*. The expression of lncRNA *CONCR* is negatively regulated by *TP53* and activated by *MYC*. *CONCR* binds its neighboring gene, *DDX11*, and enhances the ATPase activity of DDX11, thereby impairing sister chromatid cohesion, cell division, and proliferation [31]. *TP53* also regulates lncRNAs involved in DNA damage. *DINO* is induced by DNA damage in a *TP53*-dependent manner. Conversely, *DINO* stabilizes *TP53* by binding the protein and regulates *TP53*-dependent gene expression, cell cycle arrest, and apoptosis in response to DNA damage [32]. The lncRNA *LINP1* is indirectly regulated by *TP53*. Interestingly, *LINP1* expression can be activated by EGFR signaling and blocking *LINP1* increases triple-negative breast cancer (TNBC) sensitivity to radiotherapy. *LINP1* enhances double-strand DNA break repair via the non-homologous end joining pathway by linking Ku80 and DNA-PKcs. [33]. Furthermore, a recent study shows that RAS signaling regulates the expression of a group of lncRNAs. One of the targeted lncRNAs, *Orilnc1*, is highly expressed in *BRAF*-mutant melanoma and acts as a mediator of RAS/RAF activation [34].

The regulatory network between lncRNAs and protein-coding genes suggests their key roles in cancer development. Like their protein-coding counterparts, lncRNAs can act as oncogenes or tumor suppressors. They appear to participate in almost every cancer-related process, including cell proliferation, differentiation, metastasis, immune responses, metabolism, apoptosis, and genome stability. Novel cancer-associated lncRNAs have recently been characterized for different cancer phenotypes. Several lncRNAs with diverse molecular mechanisms modulate metastasis in melanoma [35], breast [36,37] and gastric cancers [38]. The lncRNAs *LINK-A* [39] and *NRCP* [40], which are highly expressed in TNBC and ovarian cancer, respectively, promote glycolysis and tumor growth. Depletion of the lncRNA *SNHG5* induces cell cycle arrest and apoptosis in colorectal cancer cells [41]. By acting as a molecular decoy, the DNA damage-induced lncRNA *NORAD* regulates genome stability by sequestering PUMILIO and inhibiting PUMILIO-mediated mRNA degradation. Identification of this lncRNA provides evidence for an unexplored role of lncRNAs in modulating genome stability [42]. Although lncRNAs can influence the immune system, little is known about immune-related lncRNAs in cancer. One recent example, *Inc-EGFR*, is upregulated in tumor-infiltrating lymphocytes in hepatocellular carcinoma patients. High *Inc-EGFR* expression leads to regulatory T cell differentiation and cytotoxic T lymphocyte inhibition in an EGFR-dependent manner, thus promoting hepatocellular carcinoma immune evasion [43].

LncRNAs for cancer diagnosis and therapy

Their aberrant expression in cancer, striking tissue specificity, and versatile regulation network, in combination with their sheer quantities, suggest that lncRNAs could represent a new class of diagnostic markers and therapeutic targets for cancer. The first prominent example of an lncRNA as a cancer biomarker is *PCA3* [44]. The Food and Drug Administration has approved the testing of patient urine samples for *PCA3* for the detection of prostate cancer. Compared to the widely used serum PSA testing, the noninvasive *PCA3* test is more specific and accurate. Other lncRNA biomarkers have been identified in hepatocellular carcinoma [45] and gastric cancer [46] patients.

In addition to their use as diagnostic markers, lncRNAs are being targeted for cancer therapy. One of the main strategies is using small interfering RNAs to inhibit lncRNA expression. This method is limited by the intracellular localization of some lncRNAs. For those located in the nucleus, modified antisense oligonucleotides (ASOs), which induce RNase H-dependent degradation or sterically block lncRNA activity, can be applied. Unlike siRNAs, ASOs can be subjected to more extensive chemical modifications, such as the addition of 2'-*O*-methyl and locked nucleic acids at both their 5' and 3' ends, to increase their stability. A recent preclinical study demonstrated the use of an ASO in a mouse breast cancer model. The ASO-induced reduction of lncRNA *MALAT1* in this metastatic luminal B breast cancer model slowed tumor growth and, remarkably, induced a cystic, poorly metastatic tumor phenotype [47]. Additionally, ribozymes or deoxyribozymes can be utilized when siRNAs or ASOs cannot be designed (due to short length or secondary structure) [48]. These RNA-based therapeutic technologies are promising, but remain limited currently. Particularly, targeting lncRNAs in vivo is challenging because of the relatively poor stability and intracellular uptake of siRNAs and ASOs. New technologies,

including biocompatible nanoparticle-based delivery, should be developed to overcome these problems [49]. Alternatively, since massive lncRNAs are capable of protein binding, especially with the chromatin modification complex, disrupting the interactions of lncRNAs with their binding partners is also a therapeutic strategy.

A group of lncRNAs has also been reported to be related to drug responses and resistance. The expression of *NEAT1* isoform 2 predicts responses to chemotherapy in ovarian cancer patients. Targeting it sensitizes cancer cells to chemotherapy [50]. Another lncRNA, lncARSR, promotes sunitinib resistance in renal cell carcinoma and correlates with poor sunitinib responses in patients. Intriguingly, this lncRNA can be incorporated into exosomes, through which it disseminates sunitinib resistance to sensitive cells [51]. In addition, *CCAT1* predicts BET inhibitor sensitivity in colorectal cancer [52], and *LINK-A* sensitizes breast cancer cells to AKT inhibitors [53]. These findings indicate the potential of using lncRNAs to predict drug responses and guide patient selection in clinic. Furthermore, the combination of chemotherapy and lncRNA targeting can be “synthetic lethal,” thereby providing advantages for cancer therapy.

Conclusions

The discovery of noncoding RNAs, especially lncRNAs, profoundly advanced our knowledges of cancer biology and the strategies for developing cancer diagnosis and therapy. Here, we discussed the current findings on the annotation and functional characterization of cancer-associated lncRNAs, their genomic alterations and differential expression in the context of cancer, and their applications in the clinic. Nonetheless, our understanding of lncRNAs is still in the early stages. Their huge variety and low abundance make it difficult to infer the functions of lncRNAs by dissecting individual examples. Recently, using FANTOM5, Hon et al. [54] generated a comprehensive atlas of human lncRNAs with high-confidence 5' ends and their expression profiles across 1,829 samples from the major human primary cell types and tissues. It further elucidates the functional potential of lncRNAs and is a valuable resource for future lncRNA research. lncRNAs hold great promise for novel therapeutic applications and, therefore, should be more thoroughly investigated in future studies. For example, given that the secondary structures of lncRNAs are crucial to their functions, investigations into lncRNAs structures require attention. Moreover, although lncRNA genes are less conserved than protein-binding genes, the development of genetic animal models, like knockout mouse models of lncRNAs [55], will help us better understand their functions in vivo.

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Figure 1. The major molecular mechanisms of lncRNAs

A. LncRNA as competitive endogenous RNAs. B. LncRNA binds to mRNA, represses translation and degradation of targeted mRNA. C. LncRNA serves as scaffold, e.g. recruits chromatin modification complex. D. LncRNA acts as decoy. E. LncRNA guides protein to specific location. F. LncRNA (e.g. enhancer RNA) tethers transcription factors to promoter region.

Table 1

Selected cancer-related lncRNAs

LncRNA	Cancer type	Function in cancer	Mechanism	Ref
BCAL8	Breast/Ovarian/Endometrial	Promotes proliferation, associated with survival of breast cancer patients	Induces G1 cell cycle arrest by affecting target genes like cyclinE2	18
SAMMSON	Melanoma	Promotes survival, sensitizes melanoma to MAPK-targeting therapy when knocking down	Regulates mitochondrial function by binding to p32, increases its pro-oncogenic function	19
CCAT2	Colorectal	Regulates metabolism in allele-specific manner	Binds to Cleavage Factor I complex, then regulates alternative splicing of GLS	20
LINC00673	Pancreatic	Inhibits cell proliferation	Promotes PTPN11 degradation, regulates SRC-ERK and STAT1 signaling	24
CONCR	multiple	Required for cell division, proliferation and sister chromatid cohesion	Interacts with DDX11 and enhances the ATPase activity of DDX11	31
LINP1	Breast	Regulates NHEJ activity, modulates sensitivity of radiotherapy response	Links Ku80 and DNA-PKcs, increases activity of NHEJ pathway and enhances DSB repair	33
SLNCR1	Melanoma	Increases Melanoma Invasion, associated with survival	Increases the binding of AR to MMP9 promoter	35
NKILA	Breast	Suppresses metastasis, represses cancer-associated inflammation	Binds to NF- κ B/I κ B complex, masks the phosphorylation sites of I κ B and stabilizes the complex	36
MAYA	Breast	Promotes metastasis, correlate with poor outcome	Mediates ROR1-HER3 and the Hippo-YAP pathway crosstalk	37
GCInc1	Gastric	Promotes proliferation and metastasis	Acted as scaffold for WDR5 and KAT2A complexes, modulates histone modification of target genes	38
LINK-A	Breast	Promotes tumor growth and glycolysis	Mediates HIF1 phosphorylation, leading to normoxic HIF1 stabilization	39
	Breast	Confers resistance to AKT inhibitors	Binds to AKT, promotes AKT-PIP3 interaction and the enzymatic activation of AKT	52
NRCP	Ovarian	Promotes proliferation, metastasis and glycolysis	Enhances interaction of STAT1 and RNA pol II, increasing STAT1 transcriptional activity	40
SNHG5	Colorectal	Upregulated in colorectal cancer, promotes survival	Stabilizes target transcripts through blocking their degradation induced by STAU1	41
lnc-EGFR	Hepatocellular	Promotes hepatocellular carcinoma immune evasion	Binds to and stabilizes EGFR, increases activities of EGFR/API/NF-AT1	43
NEAT1	multiple	Predicts chemotherapy response	Promotes ATR signaling and engaged in negative feedback loop for p53 activity	49
lncARSR	Renal	Promotes sunitinib resistance, transfers to sensitive cells through exosomes	Act as ceRNA of AXL and c-MET by binding miR-34/miR-449	51