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REVIEW ARTICLE

Long noncoding RNAs as diagnostic biomarkers associated with cancer phenotypes

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Abstract

Increasing evidence suggests that long noncoding RNAs (lncRNAs) play vital roles in the transformation and maintenance of cancer phenotypes and have important clinical implications. These lncRNAs control important aspects of tumor biology, including proliferation, angiogenesis, metastasis, and the microenvironment by regulating RNA and protein interactions or through their ability to base pair with RNA and DNA. In this study, we review the mechanism of the function of lncRNAs in cancer and their diagnostic roles in cancer phenotypes, which make them attractive as non-invasive biomarkers from body fluid samples for different types of cancer.

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Carcinogenesis is regarded to comprise genetic or epigenetic alterations that are based on two constituent processes, the continuous acquisition of heritable genetic variation in individual cells by random mutation and natural selection acting on the resultant phenotypic diversity. Furthermore, several important studies suggest that cancer is a disease of the genome, which comprises heterogeneous clonal expansions driven by the accumulation of mutations that are preferentially selected by the tumor microenvironment [1]. Many of these mutation sites overlap regions of the genome that lack protein-coding capacity. These abnormalities have an impact on noncoding RNA molecules, which display altered expression and disrupted functions in terms of regulation of their targets.

Approximately, 19,000–20,000 human protein-coding genes have been estimated to be present in the human genome. Protein-coding sequences make up only a small fraction of the genome (no more than 2%), and a large number of sequences are associated with non-coding RNA moleculars. Among noncoding RNAs, long noncoding RNAs (lncRNAs), with a length > 200 bp, have increasingly been recognized to play vital roles in tumor biology, representing a new focus in the study of cancer. Emerging technologies are expanding investigators' abilities to functionally annotate cancer-associated lncRNAs. Importantly, cancer-specific expression of certain lncRNAs has provided the necessary impetus to lncRNA research and highlighted the importance of these molecular modulators, which has been verified in the pathological states of carcinogenesis [2]. With regard to their role in cancer, lncRNAs show tissue-specific expression in a specifically regulated manner, in correlation with distinct gene sets that influence cell cycle regulation, survival, immune response, or pluripotency, among other functions, which determine the transformed phenotype of the cancer cells. In fact, lncRNAs play an important role in regulating gene expression at various levels, including chromatin, modification, transcription, and post-transcriptional processing [3–4]. Conversely, several lncRNAs are also transcriptionally regulated by key tumor suppressors or oncogenes. For example, lncRNA p21 is mediated by p53-dependent transcriptional responses, which affect the expression of hundreds of gene targets enriched for the gene sets normally repressed by p53 [5]. Zheng et al. also demonstrated that the oncogenic transcription factor cMyc is partly responsible for lncRNA expression [6]. The regulatory function occurs in many types of cancer that are involved in the specific genomic context of divergent transcription. In particular, recognition of the roles lncRNAs has revealed new diagnostic and therapeutic targets. LncRNAs appear to be more structured and stable than mRNA transcripts, the

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measurement of lncRNAs as free nucleic acids could trace cancer metastases or circulating cancer cells in body fluids, such as blood and urine. For example, the overexpression of the lncRNA *HOTAIR* promotes the metastasis of breast cancer cells by epigenetically silencing the developmentally important genes in the *HOXD* cluster [7–8]. In addition, panels of lncRNAs have already been put to good use in clinically approved tests for bladder, prostate, and non-small lung cancer [9–11]. LncRNAs are thus functional transcripts that contribute to the hallmarks of cancer. Further research into the relationship between cancer and the roles of lncRNAs will be crucial to understand and realize their therapeutic potential.

In this work, we provide an overview of the current state of lncRNA biomarker identification in cancer phenotypes linked to invasion/metastasis, angiogenesis, genome instability, and tumor-promoting inflammation.

Molecular background of lncRNAs

The catalog of lncRNAs has gradually increased in recent years. An lncRNA can be placed into one of approximately five broad categories, including sense, antisense, bidirectional, intronic, and intergenic lncRNAs [12]. According to LNCipedia2.0, the latest version of the lncRNA database, there are already 32,183 human annotated lncRNAs; however, few lncRNAs have been functionally validated [13]. Therefore, it should be elucidated theoretically as to whether most of these lncRNAs result from transcriptional noise. To answer this question, a study by Ponjavic *et al* analyzed 3122 long and full-length noncoding RNAs that exhibited signatures of functionality that are more usually associated with protein-coding genes [14]. Furthermore, Dinger *et al* have constructed a database that should provide the expression status and other valuable resources for mammalian lncRNAs [15]. Most recently, TANRIC, an open-access web resource, providing interactive exploration of lncRNAs in cancer, was constructed to characterize the expression profiles of lncRNAs in large patient cohorts of 20 cancer types, based on the Cancer Genome Atlas (TCGA) and independent datasets [16].

LncRNAs are much longer than microRNAs, and thus have a complex secondary structure, which endows lncRNAs with the ability to bind protein, RNA, and/or DNA partners. Thus, they can have several regulatory capacities, for example as activators, decoys, guides, or scaffolds for their interacting proteins, including behaving as transcription factors and histone modifiers. In the present review, we summarize the mechanism of lncRNAs' regulatory cellular processes that rely on interactions with cellular macromolecules.

Chromatin-bound lncRNAs

Chromatin remodeling was one of the first identified functions of lncRNAs. An lncRNA is generated by antisense transcription from the fibroblast growth factor receptor 2 (*FGFR2*) locus, which promotes cell-specific alternative splicing via modulation of the chromatin signature [17]. Meanwhile, prostate cancer associated 3 (*PCA3*) also is an antisense intronic lncRNA that controls the expression level of prostate cancer suppressor prune homolog 2 (*PRUNE2*) via formation of a double-stranded complex, after which the adenosine deaminase, RNA specific (ADAR)-mediated RNA editing mechanism downregulates the expression of its target gene [18]. The X-linked lncRNA Firre, helps to position the inactive X chromosome near the nucleolus and preserves one of its main epigenetic features [19]. Meanwhile, during X chromosome inactivation, lncRNA RepA can silence the expression of polycomb repressive complex 2 (*PRC2*), the mechanism of which involves the interaction between histone methyltransferase and the lncRNA 18. Conversely, lncRNAs can organize chromatin domains to coordinate long-range gene activation, such as in the case of HOTTIP and CCAT1-L, which regulate chromosome looping in their proximity to deposit activating H3K4me3 marks on gene promoters [20–22]. Importantly, recent work reported that lncRNA recruitment to distant promoters and enhancers functionally modulates cancer transcriptional programs. Such RNAs make an important contribution to the maintenance of certain transcription factors (TFs) at gene regulatory elements, which produces a positive-feedback loop that contributes to the stability of gene expression programs [23].

LncRNA and DNA methylation cooperate in the epigenetic regulation of the cancer genome

Epigenetic changes in malignant diseases have been described, such as DNA hypermethylation on CpGs islands or genetic control physical domains at several tumor-suppressor genes, oncogenes, and DNA repair genes. In addition, hypermethylation is associated with aberrant post-translational modifications on histone tails, as well as lncRNAs patterns and their levels of expression. Important evidence is provided by the lncRNA HOTAIR and its functional histone mark H3K27me3, which is directly associated to the expression level of PRC2 [24]. This function is based on a fundamental role of lncRNAs, as molecular guides or scaffolds that cooperate with methylation signals, acting as a decoy mechanism to control regional epigenetic changes throughout the human cancer genome.

LncRNAs interact with target proteins as scaffolds to modify their stability

Interactions between lncRNAs and proteins have significant effects. Interestingly, many lncRNAs exert their unique activities in cancer cells. Using RNA immunoprecipitation, two prostate-specific lncRNAs, PCGEM1 and PRNCR1, were found to associate with the androgen receptor in prostate cancer cells and cause ligand-independent activation of cell proliferation [25]. Similarly, CTBP1-AS and CCTA2 interact with TFs to modify their activity [26–27]. Furthermore, the lncRNA HOTAIR serves as a scaffold that forms a complex with Hepatitis B virus X-interacting protein (HBXIP) and lysine demethylase 1A (LSD1) to activate transcription of c-myc targeted genes [28].

LncRNAs serve as regulators of mRNA expression

Emerging evidence supports the view that lncRNAs play vital roles in the control of mRNA stability, splicing, and translation. Previously, Tripathi *et al* demonstrated that MALAT1 regulates alternative splicing by modulating the phosphorylation of SR splicing factor *in vitro* [29]. Furthermore, the lncRNA, antisense to zinc finger E-box binding homeobox 2 (*ZEB2*), regulates the expression of its target gene by impaired splicing of the internal ribosome entry site contained in an intron during epithelial–mesenchymal transition (EMT) [30]. In addition to alternative splicing, MALAT1 can also interact with pre-mRNA that directs itself to localize at the proximal chromatin region of transcriptionally active genes [31]. In addition, some lncRNAs form DNA-RNA triplexes that regulate the expression of oncogenes, such as sphingosine kinase 1 (*SPHK1*) and transforming growth factor beta (*TGFB*) via antisense orientation to their promoters [32–33].

Taken together, research has shown that lncRNAs perform functional interactions or combinations with DNA, RNA, and protein, which suggest that lncRNAs served as a multifunctional tool in several biological processes. Next, we discuss the relationship between lncRNAs and the phenotype of carcinogenesis, to further determine their contribution to cancer hallmarks.

The contribution of lncRNAs to cancer hallmarks

Hanahan and Weinberg defined the hallmarks of cancer as acquired functional capabilities that allow cancer cells to survive, proliferation, and metastasis in 2011 [34]. Two prominent characteristics of tumorigenesis were emphasized in that paper: The development of genomic instability and the tumor microenvironment. Recently, lncRNAs have been identified as, key molecular players in proliferation, viability, angiogenesis, and metastasis [35–36]. In addition, other new signatures of lncRNAs are emerging.

Modulating proliferative signaling

Cancer cells, by deregulating proliferative signals, become masters of their own proliferative destinies. Numerous studies have demonstrated that cancer-related changes in lncRNA expression could promote cancer growth, mainly by acquiring pro-growth signals and evading the growth suppressive signals.

Multiple lncRNAs are involved in the regulation of critical cell cycle regulators, such as cyclins, cyclin dependent kinases (CDKs), and p53 [37]. For example, the cyclin D1 lncRNA specifically binds with an RNA-binding protein, TLS (translocated in liposarcoma), and exerts transcriptional repression through histone acetyltransferase inhibitory activity [38]. The lncRNA ANRIL binds to and recruits PRC2 to repress the expression of p15 (cyclin dependent kinase inhibitor 2B (CDKN2B)) [39].

The lncRNA PANDA confines cells to their existing proliferative state by repressing the transcription of senescence-promoting genes, which represents a stable cell cycle arrest that limits the proliferation of pre-cancerous cells [40]. In a DNA damage-dependent manner, lncRNA Gadd7 binds to the TAR DNA-binding protein, and further modulates the expression of CDK6 at the post-transcriptional level by its altering mRNA stability [41]. Meanwhile, the expression of lncRNA HEIH in HBV-hepatocellular carcinoma is associated with recurrence and is an independent prognostic marker for survival, the mechanism of which involves G0/G1 arrest [42]. Importantly, MALAT1, an mRNA splicing mediator, is upregulated in several human cancers and contributes to cancer cell proliferation [29, 37]. The underlying mechanism is that MALAT1 promotes cellular proliferation by modulating the pre-mRNA processing of cell cycle-regulated transcription factors, such as Mybl2, an oncogenic transcription factor involved in G2/M progression [43]. In addition, Zhang *et al* demonstrated that p53 is significantly downregulated by the lncRNA ROR, which suppresses p53 translation through direct interaction with a heterogeneous nuclear ribonucleoprotein [44]. Furthermore, Myc transcription is activated in *cis* by the colon cancer-associated lncRNA CCAT1, which facilitates the long-range interaction between Myc and an enhancer element [45]. Inversely, Myc also targets numerous lncRNAs for transcriptional regulation [6], which in turn regulates cell-cycle

progression.

Inducing angiogenesis

Normally, as part of physiological processes such as wound healing and female reproductive cycling, angiogenesis is turned on, but only transiently. In contrast, during tumor progression, an "angiogenesis switch" is almost always activated and remains on [34]. The best-known angiogenic switch is vascular endothelial growth factor (VEGF). Recently, transcription of *VEGF* was identified to be modulated by multiple lncRNAs. LncRNA PVT1 is upregulated and is significantly associated with high-microvessel density and poor prognosis in gastric cancer. The mechanism of PVT1-mediated angiogenesis involves in evoking the signal transducer and activator of transcription 3 (STAT3)/VEGF-A signaling axis [46]. Similarly, lncRNAs MVIH, MIAT, and SUMO1P3 have also been reported to promote the expression of *VEGF* [47–49]. Furthermore, lncRNA GATA6-AS is upregulated in endothelial cells during hypoxia. A compelling body of evidence indicates that GATA6-AS interacts with the epigenetic regulator lysyl oxidase like 2 (LOXL2) to regulate endothelial gene expression via changes in histone methylation [50].

Influencing invasion and metastasis

The multistep process of invasion and metastasis has been conceived as a sequence of discrete steps, often termed the invasion-metastasis cascade [51], the beginning of which is EMT. During this developmental regulatory program, the transformed epithelial cells can acquire the ability to invade, resist apoptosis, and disseminate [52]. With recent advances in transcriptome analysis technologies (such as RNA-seq), emerging evidence shows that lncRNAs that are differentially expressed in tumors correlate their metastatic properties, especially EMT. Some lncRNAs, such as ATB, stabilize interleukin 11 (*IL11*) mRNA, and elevated IL-11 secretion, which induces EMT and invasion [53]. Moreover, ATB also serves as an independent prognostic marker in gastric [54] and colorectal cancer [55]. Kim *et al* reported that there is a long-range interaction and correlation between a Myc enhancer and the promoter of the lncRNA CARLo-5 [45], which has some effects on EMT, and predicts outcome in patients with hepatocellular carcinoma [56]. In contrast, the lncRNA Gas5 was reported to be a negative regulator of survival and proliferation of several cancers [57]. Low expression of Gas5 correlates with poor prognosis of breast cancer and head and neck squamous cell carcinoma [58]. In line with this, Zhao *et al* indicated that Gas5 suppresses the migration of glioma cells by downregulating the expression of microRNA miR-222 [59]. With the growing number of studies on the association of lncRNAs with metastatic properties, the potential of these types of lncRNAs as therapeutic targets and prognostic markers will be a topic of active research.

Table 1 Example biomarkers of cancer-associated lncRNAs

LncRNA	Description	Functions in tumor cells	Involved Mechanism
ABT [53–55]	Activated by TGF-beta	Metastasis ↑	RNA-RNA activation / translational regulation
ANRIL [39, 70–75]	Antisense lncRNA in the INK4 Locus (CDKN2B-AS)	Proliferation ↑ , Metastasis ↑	Chromatin remodeling
BANCR [76–78]	BRAF regulated lncRNA	Proliferation ↑ , Metastasis ↑	Transcriptional activation
BCAR4 [79–82]	Breast cancer antiestrogen resistance 4	Proliferation ↑ , Metastasis ↑	Binding to transcription factor / Transcriptional activation
CARLo-5 [45, 56]	Active regulator region of lncRNA	Proliferation ↑ , Metastasis ↑	RNA-DNA interaction /Binding to enhancer region of MYC
CCAT1/ CCAT2 [20, 26]	Colon cancer specific transcript 1/2	Proliferation ↑ , Metastasis ↑	Chromatin remodeling /Transcriptional activation
DINO [83]	Damage Induced lncRNA via p53	Proliferation ↓	Activation of p53 target genes in response to DNA damage
MVIH [49]	LncRNA associated with microvascular invasion	Angiogenesis ↑ ↑	Unknown
PVT1 [46]	STAT3-responsive lncRNA	Angiogenesis ↑	The binding of PVT1 activated the STAT3 signaling pathway
PACER [66]	P50-associated COX-2 extragenic RNA	Proliferation ↑ , Metastasis ↑ , Inflammation ↑	Activation-competent NF-kappa B p65/p50 dimers

Regulating the tumor-associated inflammatory response

As is well known, the relationship between inflammation and carcinogenesis is analogous to that between "fuel and fire" [60]. Inflammation is demonstrably capable of fosteringthe development of incipient neoplasias into cancers. It is increasingly clear that lncRNAs control the key aspects of immunity such as production of inflammatory mediators, differentiation and immune cell recruitment through regulating protein-protein or RNA-DNA interactions [61]. Recently, the roles of lncRNAs in controlling NF-κBsignaling have attracted much attention [62]. Lethe, a pseudogene lncRNA, is selectively induced by proinflammatorycytokines via NF-κB, and functions in negative feedback signaling to NF-κB [63]. During the activation of macrophages, lncRNA Tnfaip3 acts as a coregulator of NF-κB to modulate inflammatory gene transcription via epigenetic chromatin remodeling [64]. In addition, NKLIA is upregulated in breast cancer cells by NF-κB, binds to NF-κB/IκB, and directly masks of phosphorylation motifs of IκB [65]. COX-2, an important oncogenehas been linked to development, progression, and outcome of several types of human cancer.Krawczyk *et al*. identified the COX-2-lncRNA,PACER occludes NF-κB subunit p50, potentially facilitating interaction with activation competent NF-κB p65/p50 dimers [66]. Furthermore, lncRNA TCF7 is required for liver cell stem cell self-renewal and tumor proliferation. Mechanistically, TCF7 recruits the SWI/SNF complex to the promoter of TCF7 to regulate its expression, leading to activation of Wnt signaling [67]. Interestingly, Zhou *et al*. validated immune associated lncRNAs signature, which is significantly linked to the clinical molecular subtypes and prognosis in diffuse large B cell lymphoma [68].

Conclusion

Overall, increasing evidence suggests that lncRNAs play vital roles in the transformation and maintenance of cancer phenotypes, and have important clinical implications. Actually, the function and characteristics of lncRNAs have made them a well suitedcandidate for cancer molecular diagnosis (summarized together in Table 1). Importantly, lncRNAs show more tissue specificity compared to protein-coding mRNAs and miRNA[69], making them attractive in the search of novel non-invasive diagnosticbiomarkers from body fluid samples. In the future, more studies will be performed to evaluate the diagnostic value of lncRNAs in different types of cancer.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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