

Long Non-Coding RNAs in Cancer: Diagnostic and Prognostic Value

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Abstract

Long non-coding RNAs (lncRNAs) are transcripts of more than 200 nucleotides in length with limited protein coding potential were found to be pervasively transcribed and are associated with tumorigenesis due to their various functions in transcriptional, posttranscriptional and epigenetic mechanisms of gene regulation. lncRNAs are found to be differentially expressed in various cancers and associated with cancer development and progression, revealing their potential for diagnostic and prognostic biomarkers in cancer. In this review, we will summarize the most important lncRNAs, focusing on their diagnostic and prognostic potential in different cancers.

Keywords: Long non-coding RNAs; Cancer; Prognostic biomarkers; Gene expression

Introduction

Control of cell functions is regulated by gene expression, which depends on numerous proteins and non-protein coding RNAs (ncRNAs). ncRNAs have been identified as gene expression modulators, having different functions and targets [1,2]. Diverse classes of ncRNA are being studied. These molecules can be broadly classified into two groups, one being small non-coding RNAs, such as microRNAs, and the other being long non-coding RNAs (lncRNAs), subdivided into long intergenic lncRNAs, intronic lncRNAs, sense lncRNAs, antisense lncRNAs, bi-directional lncRNAs, promoter-associated lncRNAs, enhancer lncRNAs and natural antisense transcriptions (Figure 1).

Various cancer types exhibit deregulated levels of different lncRNAs. Some are deregulated in many types of cancer, while others are specific in expression in specific type of tissue. Therefore, lncRNA are an interesting field of new cancer biomarkers, for either a detection of a certain type of cancer, or for progression of cancer.

lncRNA Valuable as Diagnostic and Prognostic Biomarkers

HOX Antisense Intergenic RNA (HOTAIR) was shown to be deregulated in many types of cancers, including lung cancer, breast cancer, and cancers of the digestive tract [3]. HOTAIR is most valuable as prognostic biomarker, especially for identification of metastatic potential [4]. Upregulated expression was observed in patients with colorectal cancer, where a probable five-year overall survival is 55% compared to 80% in patients with lower levels of HOTAIR in tumor tissue [5]. Upregulation of HOTAIR was associated with lower survival rate and decrease of metastasis-free survival rate in patients with breast cancer, compared to those with lower expression values of HOTAIR [6]. In hepatocellular carcinoma (HCC) and HCC patients with liver transplantation, the expression of HOTAIR when compared with ordinary liver tissue are upregulated. Expression levels of HOTAIR can also be used as an independent prognostic marker for HCC recurrence and lower survival rate [7]. HOTAIR can be used as potential biomarker for the existence of lymph node metastasis in HCC [8]. These researches support the role of HOTAIR lncRNA as a metastazation biomarker.

MALAT1 was the first lncRNA associated with high metastatic potential and poor patient prognosis during a comparative screen of non-small cell lung cancer patients with or without metastatic tumors [9]. Although it is expressed in normal tissues but it was found to be deregulated in many cancers. Its overexpression was observed in colorectal cancer, lung cancer, gastric cancer, prostate cancer and HCC [9-14]. It has been shown that increased expression of MALAT1

can be used as a prognostic marker for HCC patients following liver transplantation [15]. Research on colorectal cancer showed significant inverse correlation with disease-free and overall survival. Patients with high expression levels were compared to those patients, which expressed lower levels of MALAT1 expression. For higher levels the five-year survival rate was 48% and overall survival was 67%, for lower levels the rates were 67% and 85%, respectively [16]. Expression levels of MALAT1 have a prognostic potential, correlating its levels to poor outcome for patients with cancer [17].

Prostate Cancer Associated 3 (PCA3) has been shown to be upregulated in prostate cancer tissue [18,19]. IT was also shown that PCA3 is highly specific for prostate cancer, since it was not detected in other types of cancer [18]. The evidence suggests that PCA3 is specific biomarker for prostate cancer.

PCGEM1 is also a prostate-specific transcript, and expressed just in prostate. The expression is upregulated in prostate cancer tissue, compared to normal [20]. Although specific for prostate cancer, there has not been found an association between levels of PCGEM1 and patient survival rates [21].

Urothelial cancer associated 1 (UCA1) was found to be a potential biomarker for bladder cancer [22]. In tumor tissue expression of UCA1 is upregulated, and it can be detected in cellular sediment with sensitivity of 80.9% for determining the disease diagnosis. It also allows discrimination of urothelial cancer from other urinary tract diseases, such as renal cell carcinoma, upper urinary tract restriction, and neurogenic bladder, and others, with overall specificity of 91.8% [22]. It has been shown that even higher expression was detected in urine in progressive stage of urothelial cancer [23].

Highly upregulated in liver cancer (HULC) lncRNA exhibits high levels of expression in liver cancer compared to normal hepatic tissue. In cancers with higher Edmondson grade classification the expression of HULC is even higher, and correlates with disease aggressiveness, which is supporting the potential of HULC as biomarker of prognosis [24].

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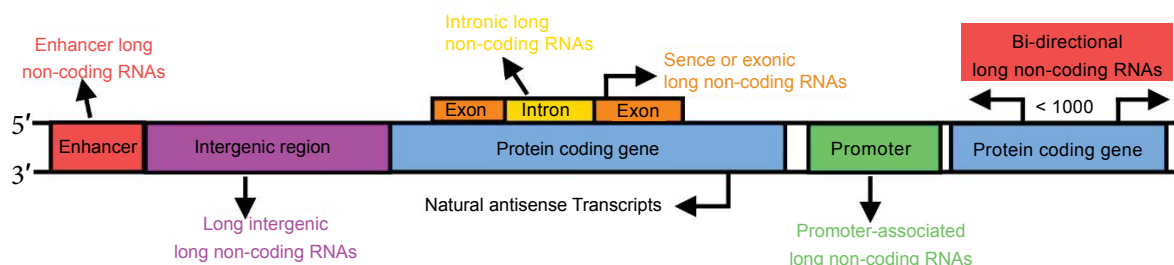


Figure 1: Illustrative representation of biogenesis of lncRNA. Various regions on the genome can produce different lncRNA, such as enhancer lncRNA, long intergenic lncRNA, intronic lncRNA, sense lncRNA, natural antisense transcripts, promoter-associated lncRNA and bi-directional lncRNA.

lncRNA	Cancer Types	Regulation	Diagnostic and/or prognostic value	References
HOTAIR	Breast, Lung, Colorectal, Hepatocellular	↑	Metastazation biomarker	[4,31]
MALAT1	Colorectal, Lung, Gastric, Prostate, Hepatocellular	↑	Poor outcome	[15,32]
PCA3	Prostate	↑	Specific for prostate cancer	[33-35]
PCGEM1	Prostate	↑	Specific for prostate cancer	[20,21]
UCA1	Urothelial	↑	Specific for urothelial cancer	[22,23]
HULC	Hepatocellular	↑	Prognosis in hepatocellular cancer	[24]
SRA	Breast, Uterus, Ovary	↑	Steroid-based tumors	[25]
MEG3	Brain	↓	Prognosis in brain cancer	[27,28]

Table 1: Diagnostic and prognostic value of cancer associated lncRNAs (adapted from Ref. [29] and Ref. [30]).

SRA is a coactivator for steroid receptors acts as an ncRNA discovered within the nucleus and protoplasm. SRA regulates process mediated by means of steroid receptors through complexing with proteins additionally containing steroid receptor coactivator one (SRC-1) [25]. The SRA1 component encrypts a peptide molecule that acts as a coactivator and corepressor [26]. SRA levels are discovered to be upregulated in breast tumors, where it can be assumed that increased SRA levels have effect on the steroid receptors', in turn contributing to breast tumorigenesis. Whereas the expression of SRA in average tissues is low, it is particularly up-regulated in tumors of the breast, uterus and ovary. This proofs that SRA might have capabilities of a biomarker of steroid-based tumors [25].

Maternally Expressed Gene three (MEG3) was found to be downregulated in glioma and, is highly expressed in normal brain tissue. It has been associated with prolonged survival of patients with glioblastoma multiforme (GBM). Overexpression of MEG3 increased apoptosis and inhibited glioma cell proliferation [27,28]. Following this evidence MEG3 has the potential for prognostic biomarker.

We have summarized all the important lncRNA with potential biomarker capabilities in Table 1.

Conclusions

The potential of lncRNA is enormous, from diagnostics to therapy. From potential of being isolated from bodily fluids, to higher sensitivity following technological improvements, lncRNA may be recognized as cancer biomarkers with true diagnostic and prognostic value [36]. The strong correlations found thus far between expression deregulation of lncRNA and cancer initiation and progression, have been the basis of prediction for targeted therapies. It was shown that lncRNAs could act as regulator of the expression of miRNA, proposing that by targeted therapy, expression of both miRNA and lncRNA can be modified [37]. While few miRNA therapeutics have been already submitted to clinical trials (miR-34, let-7), the lncRNA therapy strategies are still being developed. Inactivation of lncRNA is possible through inhibition of active site or through disruption of secondary structure, leading to loss of function. Further research on structure and functions of lncRNA will

uncover more possibilities for diagnostic and therapeutic possibilities of lncRNA.

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