



# Long Non-coding RNAs and their “orchestration” in cancers

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## ABSTRACT

The behavior of “mysterious” long non-coding RNAs (LncRNAs) in cells and in cancers is quite fascinating. Their diverse and complex functions have astonished the entire scientific community. LncRNAs are absolutely diversified in nature and can execute a decisive task to regulate the genes in conjunction with developmental processes. They emerged as “key orchestrators” in cancers because of their involvement in cell proliferation, migration, and invasion. In this precise opinion, we first discuss the role of LncRNAs in various processes in the cell, and later, we brief the participation of LncRNAs in cancers with a note on their protein-coding potential.

## 1. INTRODUCTION

Research studies revealed that the human genome encodes only 2% of protein-coding genes [1]. The pervasive transcription of the genome is leading to the generation of non-coding RNA (ncRNA) [1]. The ncRNA categorized into small ncRNA, for instance, micro-RNA (mRNA) and other class being are long ncRNAs (lncRNAs). LncRNAs are grouped into sense lncRNAs, antisense lncRNAs, intronic lncRNAs, long intergenic lncRNAs, promoter-associated lncRNAs, bidirectional lncRNAs, natural antisense transcriptions, and enhancer lncRNAs [2].

lncRNAs typically 200 nucleotides - 100 kb transcripts that lack open reading frame belongs to a team of ncRNAs [3,4]. Like, usual mRNA often codes for a protein, the lncRNAs are also spliced, capped, and polyadenylated [5]. LncRNAs possess the ability to bind to the DNA, RNA, and proteins to execute their effects on gene expression by utilizing diversified mechanisms [6].

lncRNAs regulate gene expression at transcriptional, post-transcriptional, and epigenetic levels [7]. At the epigenetic level, they regulate through RNA interference, DNA methylation or demethylation, chromatin remodeling, and histone modifications [8-14].

The lncRNAs involve in diverse functions in the cell summarized in Figure 1 [15].

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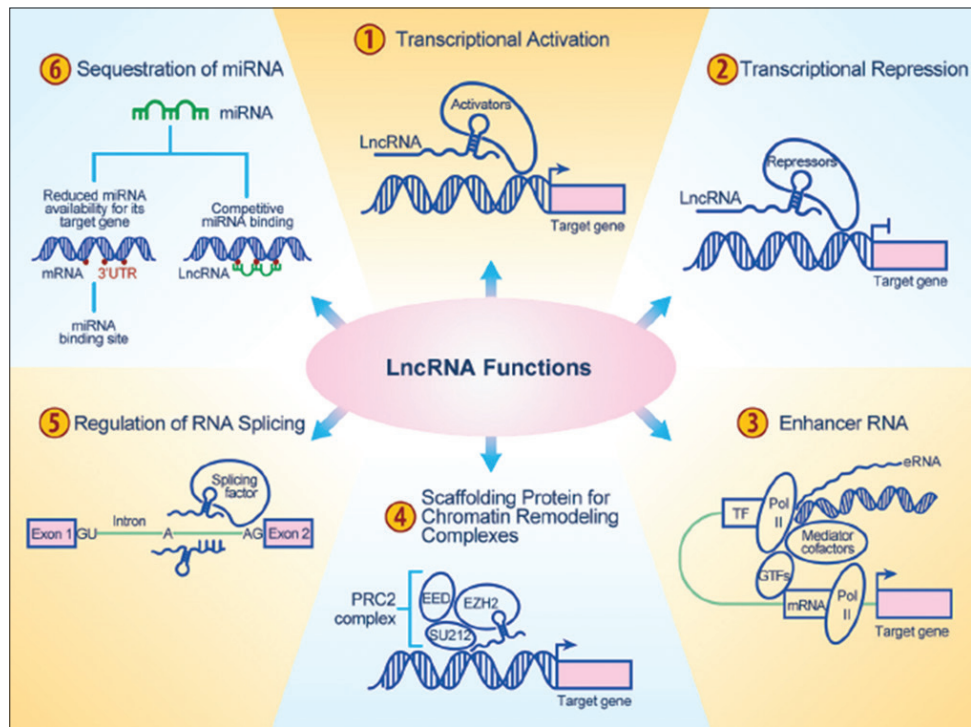
Detection of structurally complex lncRNA helped to comprehend the physiology of the cell in addition to disease pathogenesis [6]. Deregulated expression of lncRNA plays a key role in diseases [16]. Hon *et al.* [17] in their study stated that lncRNAs are unquestionably functional orchestrators in multiple diseases. Altered expression of lncRNAs in cancers as well as in other diseases was already reported [18,19]. Hence, they may serve as potential markers for therapeutic intervention in various diseases.

Research studies clearly remarked that lncRNAs incredibly heterogeneous and exhibit significant functional versatility due to their conformations they assume in the course of their developmental processes and positively assisting all of them to interact with other molecules [20]. For instance, extremely diversified lncRNA interacts with various proteins which play a decisive role in the pathogenesis of various disease conditions [21].

lncRNA also experiences mutations as like protein-coding genes in such cases they become more powerful in cancers and thereby contributing to the formation of tumors and metastasis [22]. The lncRNA inactivates major tumor suppressor genes and leads to carcinogenesis [23].

lncRNAs could display characters such as promoting cancers or suppress cancers [22]. Recently, Marin-Béjar *et al.* [24] reported a lncRNA titled LINC-PINT (long intergenic non-protein-coding RNA, p53-induced transcript) that typically behaves as a tumor suppressor, lowering the invasive character of cancer cells. In addition, they pointed out that this is achieved merely by an interaction between highly conserved sequence elements in LINC-PINT with PRC2.

Recently, discovered lncRNAs role and mechanism of action in various cancers summarized in Table 1.



**Figure 1:** Functions of long Non-coding RNAs [15]

(1) Activation of target gene happens when lncRNAs interact with transcriptional activators. (2) lncRNAs represses transcription in two ways one would be keeping transcriptional activators away from chromatin and another one would be disturbing the tumour suppressor signaling. (3) The long non-coding Enhancer RNAs recruits lineage-specific complexes and regulate signaling. (4) lncRNAs recruits chromatin remodeling complexes that include PRC1 and PRC2 and serves as scaffolding proteins. (5) lncRNAs interacts with splicing factors or splicing junctions of pre-mRNA and thereby regulating the RNA splicing. (6) lncRNAs possesses binding sites for miRNAs and occupies their mRNA targets and hence serves as molecular sponges. mRNA: messenger RNA, GTF: general transcription factors, eRNA: enhancer RNA, lncRNA: long noncoding RNA, miRNA: microRNA, PRC2: polycomb repressive complex 2, UTR: untranslated region, Pol II: RNA polymerase II, TF: transcription factors.

The above examples establish the fact that lncRNAs are “key orchestrators” in cancer progression. However, what about the proteins encoded by them? Do they have any potential to get translated into proteins? Do they play a role in cancer? This has become a topic of much debate in recent times.

Based on some studies, lncRNAs own the potential to get translated into too short peptides; this feature is observed through ribosome protection patterns [31-33]. The regions of translated transcripts can be examined using ribosome profiling which involves the sequencing of ribosome protected fragments [31].

In yeast, Wilson and Masel [34] found that novel protein-coding genes arise from non-coding sequences. According to Xie *et al.*, lncRNAs with active and regulated transcriptional properties could be the origin of the newly evolved proteins [35]. As reported by Ruiz-Orera *et al.*, there are strong similarities between lncRNA molecules and recently evolved protein-coding genes [36].

Assessing the properties of the small open reading frames (sORFs) in lncRNAs and young protein-coding transcripts, Ruiz-Orera *et al.* found that new peptides could be encoded by lncRNAs [36]. There emerges another proof from Mackowiak *et al.* that sORFs get translated and exhibits some wide conservation between vertebrates and invertebrates [37].

Recently, lncRNA LINC00961 encoded a polypeptide called small regulatory polypeptide of amino acid response which aids

in the muscle regeneration [38]. The data provided by Matsumoto *et al.*, the short proteins encoded by lncRNA can orchestrate the biological processes in line with the requirements of specific tissues [38]. Another example, myoregulin a micro peptide encoded by a putative lncRNAs known to regulate skeletal muscle physiology [39].

Aggregated data shed light on the possibility of coding potential of lncRNAs according to necessities in the cell.

In case of cancer, proteins translated from lncRNAs still to be found and consequently their role in the cancers. As stated by Ruiz-Orera *et al.*, short peptides obtained from lncRNAs undergo degradation as soon as they get translated [36]. This is the key reason which is making it so challenging to uncover the proteins encoded by lncRNAs in cancers. If this is the fact that they are synthesized in cancers, there could be a potential chance of targeting cancer.

## 2. CONCLUDING REMARKS

lncRNA research is a quite challenging area to study. Applying them to the significantly larger segments of the diseases and studying the role of lncRNA within the cells is in fact, intriguing.

At present, lncRNAs are in the discovery stage and their interventions in diseases. The lncRNAs are required to be evaluated individually to acquire knowledge of the precise function. One strategy could be using the drugs in combination in which one would suppress the expression

**Table 1:** The lncRNAs role and mechanism of action in various cancers.

lncRNA	Type of cancer	Role in cancer	Mechanism of action	Reference
AGAP2-AS1	Small lung cancer	Cell proliferation, migration, and invasion	AGAP2-AS1 attaches to the EZH2 and lysine (K)-specific demethylase 1A and forms a complex which binds to the promoter region of tumor-suppressor LATS2 and KLF2 to repress their transcription.	[19]
LINC00152	Gallbladder cancer	Cell migration, invasion, and EMT	LINC00152 binds to miR-138 and repress the HIF-1 $\alpha$ that suppresses the metastasis of gallbladder cancer.	[18]
XIST	Bladder cancer	Proliferation, invasion, and migration	XIST targets androgen receptor binding with miR-124 and facilitates proliferation, invasion, and migration.	[25]
MALAT1	Hepatocellular carcinoma	Migration and invasion	miR-204 targets SIRT1 to suppress the growth and invasion of hepatocellular carcinoma. MALAT1 attaches competitively to miR-204-SIRT1 and promotes migration and invasion.	[21]
TUG1	Gastric cancer	Proliferation	TUG1 arrests G0/G1 cell cycle and plays a key role in the regulation of proliferation of cell by silencing p57 epigenetically.	[26]
SNHG20	Non-small cell lung cancer	Cell proliferation, migration, and induced cell apoptosis.	SNHG20 suppresses P21 expression by interacting with the EZH2	[27]
HOXA11as	Serous ovarian cancer	Cell proliferation and invasion	HOXA11as regulates expression of genes such as matrix metalloproteinase 9 (MMP-9), VEGF, B-catenin, and others which are implicated in the progression of serous ovarian cancer.	[28]
SPRY4-IT1	Colorectal cancer	Larger tumor, cell proliferation, migration, and invasion	SPRY4-IT1 regulates EMT and aids in the migration and invasion.	[29]
BC200	A broad spectrum of cancers	Proliferation	Elevation of expression level leads to the proliferation.	[30]

EMT: Epithelial-mesenchymal transition, HIF-1 $\alpha$ : Hypoxia-inducible factor-1 $\alpha$ , EZH2: Enhancer of zeste homolog 2, VEGF: Vascular endothelial growth factor.

of lncRNA and another drug effectively targets tumor cell [40]. Since lncRNA works effectively utilizing diverse structures, molecules that could bind to them or alters the structure, for neutralization could be developed [40].

The investigation of lncRNAs should head toward finding their role in escalation or suppression of a disease. The emergence of advanced technologies in RNA Biology made a significant pathway to find biomarkers.

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