Long Non-Coding RNAs “Key Orchestrators” in Cancers

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Abstract

Long Non-Coding RNAs (lncRNAs) attaining impeccable attention in recent times owing to their expanded roles in the cell. They essentially perform a decisive task to regulate the genes in conjunction with developmental processes. In cancers the lncRNAs involves in the cell proliferation, migration and invasion made them as “key Orchestrators”. In this precise opinion, we brief the role of lncRNAs in cancer with a note on their protein-coding potential.

Keywords

Long Non-Coding RNA, Cancer, Cell proliferation

Research studies revealed the human genome encodes only 2% of protein-coding genes and certainly, the rest of the genome is transcribed into tiny pieces of nonprotein-coding RNAs acknowledged as noncoding RNA (ncRNAs) [1]. Noncoding RNA categorized into small noncoding RNA, for instance, micro RNA and other class being are long non-coding RNAs (lncRNAs). lncRNAs grouped into sense lncRNAs, antisense lncRNAs, intronic lncRNAs, long intergenic lncRNAs, promoter-associated lncRNAs, bi-directional lncRNAs, natural antisense transcriptions and enhancer lncRNAs [2].

Long noncoding RNAs typically 200 nucleotides–100 kb transcripts that lack open reading frame belongs to a team of noncoding RNAs (ncRNAs) [3,4]. Like usual mRNA often codes for a protein, the lncRNAs are also spliced, capped as well as polyadenylated [5]. lncRNAs possess the ability to bind to the DNA, RNA in addition to proteins to execute their effects on gene expression utilizing diversified mechanisms [6].

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

Detection of Structurally complex long non-coding RNA (lncRNA) helped to comprehend the physiology of the cell in addition to disease pathogenesis [6]. Deregulated expression of lncRNA plays a vital role in diseases [15]. Altered expression of lncRNAs in cancers as well as in other diseases were reported[16,17].

lncRNAs 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 [18].

Chung-Chau Hon *et al.*. [19] in their study stated that long noncoding RNAs are unquestionably functional orchestrators in multiple diseases. Extremely diversified lncRNA interact with various proteins which play a decisive role in the pathogenesis of various disease conditions [20].

lncRNA also experiences mutations as like protein-coding genes in such cases they become more powerful in cancers by contributing to the formation of tumours and metastasis [21]. The lncRNA inactivates major tumour suppressor genes and lead to carcinogenesis [22] lncRNAs could display characters like, promoting cancers or suppress cancers [21]. Recently Oskar Marín-Béjar *et al.* [23] reported a lncRNA titled LINC-PINT (long intergenic non-protein coding RNA, p53 induced transcript) that typically behaves as a tumour suppressor, lowering the invasive character of cancer cells. Additionally, they pointed out that this is achieved merely by an interaction between a highly conserved sequence element in LINC-PINT with polycomb repressor complex 2 (PRC2).

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

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 enhancer of zeste homolog 2 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.	[17]
LINC00152	Gallbladder cancer	Cell migration, invasion and epithelial-mesenchymal transition (EMT)	LINC00152 binds to miR-138 and repress the HIF-1 α (Hypoxia-inducible factor-1 α) that suppresses the metastasis of Gall Bladder cancer.	[16]
XIST	Bladder cancer	Proliferation, invasion, and migration	XIST targets androgen receptor binding with miR-124 and facilitates proliferation, invasion, and Migration.	[24]
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.	[20]
TUG1	Gastric cancer	Proliferation	TUG1 arrests G0/G1 cell cycle and plays a vital role in the regulation of proliferation of cell by silencing p57 epigenetically.	[25]
SNHG20	Non-small cell lung cancer	Cell proliferation, migration and induced cell apoptosis.	SNHG20 suppresses P21 expression by interacting with the enhancer of zeste homolog 2 (EZH2)	[26]
HOXA11as	Serous ovarian cancer	cell proliferation and invasion	HOXA11as regulates expression of genes like matrix metalloproteinase 9 (MMP-9, vascular endothelial growth factor (VEGF), B-catenin and others which are implicated in the progression of serous ovarian cancer.	[27]
SPRY4-IT1	Colorectal cancer	Larger tumor, cell proliferation, migration and invasion	SPRY4-IT1 regulates epithelial-mesenchymal transition (EMT) and aids in the migration and invasion.	[28]
BC200	Broad spectrum of cancers	Proliferation	Elevation of expression level leads to the proliferation.	[29]

Basing on the examples given above, it is well established that lncRNAs key players in the cancer progression, but what about the proteins encoded by them? Do they have any potential to get translated into proteins? Are they having any potential role in cancer? This topic has become a much of a debate now.

Based on some studies, lncRNAs own the potential to get translated into too short peptides, this feature is observed in the ribosome protection patterns [30], [31], [32]. The regions of translated transcripts can be examined using ribosome profiling involves the sequencing of ribosome protected fragments [30].

Wilson and Masel. [33] Found in Yeast that novel protein-coding genes arise from non-coding sequences. According to *Xie et al.*, long non-coding RNAs with active and regulated transcriptional properties could be the origin of the newly evolved proteins [34] As reported by Ruiz-Orera *et al.*, there are strong similarities between lncRNA molecules and recently evolved protein-coding genes [35].

Assessing the properties of the sORFs in lncRNAs and young protein-coding transcripts *Ruiz-Orera et al.*, found that new peptides could be encoded by lncRNAs [35]. There emerges another proof from *Mackowiak et al.*, that sORFs get translated and exhibits some wide conservation between vertebrates and invertebrates [36].

Recently, lncRNA LINC00961 encoded a polypeptide called SPAR (Small Regulatory Polypeptide of Amino acid Response) which aids in the muscle regeneration [37]. The data provided by *Matsumoto, A et al.*, the short proteins encoded by lncRNA can orchestrate the biological processes in line with the requirements of specific tissues [37]. Another example Myoregulin (MLN) a micro peptide encoded by a putative long non-coding RNA known to regulate skeletal muscle physiology [38].

Aggregated data shed light on the possibility of coding potential of long non-coding RNAs 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 undergoes degradation as soon as they get translated [35]. This must be the reason making it so challenging to uncover them. If this is the fact that they are synthesized in cancers there could be a potential chance of targeting cancer.

Concluding Remarks

Long non-coding RNA 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 Long noncoding RNAs are required to be evaluated individually to acquire knowledge of the precise function. One strategy could be using drugs in combination in which one would suppress the expression of lncRNA and another drug effectively targets tumour cell [39]. Since lncRNA works effectively utilizing diverse structures, molecules that could bind to them or alters the structure for neutralization could be developed [39].

The investigation of long non-coding RNAs should head towards finding their role in escalation suppression of a disease. The emergence of advanced technologies in RNA Biology made a significant pathway to find biomarkers.

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