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REVIEW ARTICLE

Diagnostic and Therapeutic Implication of Long non-coding RNAs in Cancer

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ABSTRACT

Long ncRNAs behave as tumour suppressors or oncogenes, and their activity can affect all cancer-related symptoms. They are readily observable in the cells or biological fluids of patients and exhibit themselves in a very constrained geographic and temporal manner. They are ideal candidates for the development of anticancer medicines because of these characteristics. In order to stop the development of cancer, targeting techniques try to reduce carcinogenic lncRNAs or interfere with their functions. It is advised to target long ncRNAs therapeutically in cancer using a variety of methods, including suppression of oncogenic long ncRNAs, modification of their epigenetic effects, interfering with their function, restoring downregulated or lost long ncRNAs, and recruitment of long ncRNAs regulatory elements and expression patterns. These methods have demonstrated inhibiting effects on cancer. Proliferation, migration, and invasion are examples of this.Rarely have effective and secure delivery methods for the pharmacological and therapeutic targeting of long non-coding RNAs in cancer been discussed. LncRNAs have only been used in one clinical trial that has been documented. RNAi is the most widely applied and efficient technology for targeting lncRNAs. To use lncRNAs in therapeutic settings, however, different technologies must be investigated, and more study is required.

Keywords: Long non-coding RNA, Cancer treatment, RNAi, siRNA,

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INTRODUCTION

Cells proliferate rapidly and uncontrollably, which finally results in the formation of tumours, and this is what causes cancer. Metastasis or mortality might result from delayed diagnosis and treatment. Cancer can arise from any circumstance that alters the expression of tumour suppressor genes or oncogenes[1].

Tiling arrays and next-generation RNA sequencing (RNA-seq), among other high throughput sequencing technologies, have made it possible to objectively examine the transcriptome's whole collection of RNA transcripts. The simplicity with which all RNA types, including microRNAs, snRNAs, snoRNAs, lncRNAs, piRNAs, and others may be identified thanks to whole transcriptome sequencing has substantially risen. Additionally, RNAs are widely divided into two groups based on length: (a) RNAs longer than 200 nucleotides (like lncRNAs), and (b) RNAs shorter than 200 nucleotides (e.g., microRNAs)[2].

Long RNA transcripts known as long non-coding RNAs (lncRNAs) are longer than 200 nucleotides and lack any protein encoding region. Since it has been discovered that there are more lncRNAs than protein-coding transcripts, research on their functions in cells and metabolism has received a lot of attention. LncRNAs can be translated, spliced, capped, and polyadenylated via the RNA polymerase II-like protein-encoding pathway, just like mRNAs. Although lncRNAs and mRNAs share some characteristics, it has been

discovered that lncRNAs have non-random short open reading frames (sORFs)[3].They play a key role in controlling biological processes such the cell cycle, proliferation, differentiation, metabolism, apoptosis, and the preservation of pluripotency[4].

Extreme somatic mosaicism, which results from the accumulation of genetic and epigenetic changes, is often the cause of cancer. Only about 2% of the human genome actively codes for proteins, despite the fact that 80–90% of genes are actively transcribed. However, non-coding portions of the human genome are also dysregulated in cancer. Protein-coding regions of the human genome are associated with a disproportionate amount of causative evidence for cancer. More than 23,000 lncRNAs, many of which play significant roles in cellular functions in both healthy and malignant cells, are found in the human genome. Despite sharing traits with mRNA, lncRNAs differ at the transcriptional level in a way that depends on the tissue and cell.Through direct interactions with nucleic acids and proteins, differently regulated long noncoding RNAs (lncRNAs) that have been linked to the emergence of cancer promote the malignant transformation process[2].

LncRNAs have important roles in the transcription of DNA, chromatin remodelling, chromosomal looping, interactions with proteins and mRNAs, and more. Therefore, abnormalities or limitations in lncRNA expression may lead to the emergence of diseases, including cancer. It is not unexpected that lncRNAs are frequently dysregulated in cancer as cancer cells exhibit unchecked proliferation and metastasis, traits that are not present in normal cells. LncRNAs can therefore be thought of as prognostic, therapeutic, and diagnostic variables in cancer[3].

This review attempts to present potential methods for therapeutically targeting long ncRNAs in cancer. It also explains how nucleic acid-based therapies can be chemically altered to enhance their pharmacological characteristics. Following a brief discussion of methods for systematic delivery of medicines into tumour cells or other organs, a description of barriers to the development of new therapies follows.

DIFFERENT TYPES OF lncRNAs INVOLVED IN CANCER

Oncogenic lncRNA

The concept of an oncogene includes nuclear enriched abundant transcript1 (NEAT1), antisense noncoding RNA in the INK4 locus (ANRIL), HOTAIR, and metastasis associated lung adenocarcinoma transcript 1 (MALAT1). The transcript HOTAIR comes from the homeobox gene (HOXC) cluster's antisense strand. It increases tumour development, invasion, metastasis, and a poor prognosis in solid tumours where it is overexpressed[5][6]. HOTAIR brings lysine-specific histone demethylase 1A (LSD1) and polycomb repressive complex 2 (PRC2) to the target gene promoters. Some tumour suppressor genes may be silenced as a result of tri-methylation at the 27th lysine residue of the histone H3 protein (H3K27me3) and demethylation at lysine 4 (H3K4)[7].

In hepatocellular and colorectal carcinomas, pancreatic tumours, ovarian cancer, and sarcomas, LncRNA HOTAIR is dysregulated. Since HOTAIR acts as a miR-148a sponge and positively controls the production of the transcription factor zinc finger protein SNAI2 (Snail2), it promotes the epithelial-mesenchymal transition (EMT) and increases cell invasion and metastasis in esophageal cancer[8][9][10][11].

MALAT1 localises the nucleus and takes involvement in both transcriptional and posttranscriptional levels of RNA splicing and gene expression. Tumor cell growth, migration, invasion, metastasis, or apoptosis are all factors. Breast, lung, bladder, esophageal squamous cell carcinoma, and glioma are only a few of the tumours for which MALAT1 is upregulated[12][13].

Tumor-suppressor lncRNA

Maternally expressed gene 3 (MEG3), growth arrest specific 5 (GAS5), neuroblastoma-associated transcript-1 (NBAT-1), and long intergenic non-protein coding RNA, P53-induced transcript (LINC-PINT) are examples of lncRNAs that also function as tumour suppressors and play important roles in cellular processes. In malignancies, they are downregulated. Inhibiting tumour invasion, LINC-PINT localises downstream of p53 and functions as its regulatory effector[14][15]. In animal models, it is downregulated, and many tumours lose the expression of LINC-PINT as a result[16]. The lncRNA MEG3 is polyadenylated. Its imprinted gene is located on chromosome 14q32.2 at the delta-like non-canonical notch ligand1-the maternally expressed gene 3 (DLK1-MEG3) locus[17].

Normal human tissue expresses MEG3 at high levels, which is induced by cyclic adenosine monophosphate (cAMP). Through interactions with several microRNAs, highly expressed MEG3 reduces tumour proliferative activity and increases tumour apoptosis[18][19]. In addition, MEG3 expression is reduced or absent in a variety of malignancies, including leukaemia, brain, lung, colon, and liver tumours. MEG3 expression is epigenetically regulated, and abnormal CpG methylation has been seen in a number

of cancer types. Transforming growth factor-b (TGF-b) pathway genes, which have an impact on cell invasion and immunological control, are modulated by MEG3. Additionally, it makes p53 active[20][21].
The expression of c-Myc is increased in renal tumours due to the down-regulation of the tumour suppressor lncRNA FILNC1, which also improves lactic acid and glucose metabolism[22].

lncRNA in cancer Diagnosis and Prognosis

Diagnosis: lncRNA as biomarker

LncRNAs have the potential to be therapeutic targets and diagnostic or prognostic biomarkers since they express differently depending on the type of cell, tissue, stage of development, or disease. Only cancer cells express a number of lncRNAs. Prostate cancer is encouraged to spread and invade by the prostate cancer antigen 3 (PCA3). Prostate cancer urine biomarker PCA3 has received approval. In comparison to the prostate-specific antigen (PSA) test, this lncRNA shows greater specificity and sensitivity. When compared to healthy prostatic tissue, it is 60–100 times more overexpressed in prostate cancers, although it is undetectable in other cancer types[23].

Prognosis: Metastasis and Survival

According to several research, lncRNA-containing tumor-derived vesicles can alter the pre-metastatic milieu to make way for DTCs. For instance, in patients with lung squamous cell carcinoma (LSCC), elevated expression of exosomal lncRNA-SOX2-OT is substantially linked with tumour size, TNM stage, and metastasis. ExosomallncRNA lymph node metastasis-associated transcript 2 (lncRNALNMAT2) has also been shown to be a therapeutic target for lymph node metastasis in bladder cancer in recent studies. These data overwhelmingly point to the likelihood that lncRNA will play useful roles in the regulation of the metastatic environment[24][25][26].

Cancer Risk Prediction

The recently discovered lncRNA known as colon cancer-associated transcript 2 (CCAT2) exhibits the rs6983267 single nucleotide polymorphism (SNP) and is expressed more frequently in colorectal cancer that is microsatellite-stable. A recent meta-analysis suggested that CCAT2 over-expression could be employed as a biomarker of metastasis and a poor prognosis in several cancer types. Over-expression of CCAT2 may be linked to a higher risk of lymph node and distant metastases, as well as worse survival rates, according to experimental data[27][28].

Prediction of Tumor recurrence

Most of the anticancer drugs cannot completely cure cancer, therefore, there is always a chance of recurrence. Recognition and detection of biomarkers that are able to detect tumor recurrence are of utmost importance. For instance, patients with bladder cancer whose tumours contain a higher proportion of lncRNA H19-expressing cells are reported to have a considerably shorter duration of disease-free survival from the initial biopsy to the initial recurrence[29][30]. Upregulation of MALAT1 after liver transplantation is also an indication of recurrence of hepatocellular carcinoma (HCC) [31]. Lower expression levels of MALAT1 suggests higher probability of breast cancer recurrence than that of higher expression levels [32][33][34].

lncRNA in Cancer Therapeutics

Directly TargettinglncRNAs

Suppression of Oncogenic lncRNAs

Since oncogenic lncRNAs are overexpressed in tumours, it is possible to target them and lower their levels by using various technologies. These methods—of which nucleic acid-based techniques have dominated—are detailed here. These technologies also enable the functional study of lncRNAs and the targeting of epigenetic changes[4].

Antisense Oligonucleotides

Antisense oligonucleotides (ASOs) are single-stranded antisense oligonucleotides containing flanking RNA nucleotides and a core DNA stretch (at least 6mers) that can be either native or phosphorothioated (chemically modified). Target lncRNA and DNA combine to produce an RNA/DNA heteroduplex, which endogenous RNaseH1 will break. ASOs have been successful in treating a number of disorders and are often employed to change mRNA expression. They can be used to suppress lncRNAs that are highly expressed in malignancies [4].

Locked Nucleic acid GapmeRs (LNA GapmeRs)

LNAGapmeRs, in terms of structure and function (16 nucleotides), are essentially similar to ASOs, with the exception that the gap DNA segment lacks the LNA while the surrounding arms of GapmeRs have the LNA chemically changed. LNA raises nuclease resistance and binding affinity. GapmeRs feature phosphothioated backbones that protect them from enzymatic deterioration[4].

Cancer type	LncRNA	Implication	Expression Level	Reference
Prostate cancer	PCA3	Routine detection of prostate cancer is made through urine test	Upregulated	[35]
Prostate cancer	MALAT1	Men with positive biopsy for this cancer have high levels of MALAT1	Upregulated	[36]
Bladder cancer	Anti-sense mitochondrial lncRNA (AsncmtRNA)	Downregulation of AsncmtRNA implies positive result for Bladder cancer	Downregulated	[37]
Oral Squamous cell carcinoma (OSCC)	HoxTanscript Antisense RNA (HOTAIR)	It is a non-invasive and rapid diagnostic tool for detecting oral cancer	Upregulated	[38][22]
Liver cancer (Intrahepatic cholangiocarcinoma)	Carbamoyl phosphate synthase-1 intronic transcript 1 (CPS1-IT1)	It is a potential prognostic biomarker for intrahepatic cholangiocarcinoma patients	Upregulated	[39]
Gastric cancer	Gastric cancer associated transcript 1 (GACAT1)	Downregulation of this biomarker implies gastric cancer	Downregulated	[40]
Gastric cancer	GACAT2	Gastric cancer can be diagnosed through expression of this marker	Downregulated	[41]
Gall bladder cancer	Colon cancer associated transcript 1 (CCAT1)	Gall bladder cancer be detected through expression levels of this lncRNA	Upregulated	[39][25]
Breast cancer	MALAT1	This lncRNA acts a prognostic biomarker for the detection of breast cancer	Downregulated	[32][42]
Breast cancer	LI NC00705, LINC00310, LINC00704, HAR1A, etc	Increased expressions of these biomarkers imply recurrence	Upregulated	[43]
Breast cancer	HOTAIR	Potential biomarker for prognosis and diagnosis of breast cancer	Upregulated	[44]
Breast cancer	CCAT2	Promotes oncogenesis of triple negative breast cancer	Upregulated	[45]

Table 1: lncRNAs used in Cancer Therapeutics

Mixmer

Mixmers are composed of many kinds of monomers and chemically modified nucleotides, such as LNA. They lack regular sequential DNA nucleotides and are not an RNase H1 substrate. As a result, they sterically prevent nucleic acids, ribonucleoproteins, or lncRNA from linking together. They can be employed to stop epigenetic remodelling complexes, modify pseudogene-regulated gene expression, reroute alternative splicing, fix damaged RNA, and restart protein synthesis[46].

Small interfering RNAs (siRNAs) and Short hairpin RNAs (ShRNAs)

Using siRNA, or small interfering RNA, is a knockdown technique.

Short double-stranded RNAs are known as siRNAs. They separate into single strands, join with the RNA-induced silencing complex (RISC), and form a base pair with an interesting lncRNA, which causes the target transcript to be degraded by argonaute[47][48].

Short hairpin RNA (ShRNA) is a type of RNAi which show expression inside of cells. When compared to endoribonuclease-made siRNA (esi-RNAs), ShRNAs have a significantly greater off-target effect and produce silencing responses that may be temporary or sustained. Plasmid vectors containing shRNA or siRNA are used to transfect tumour cells[49].

Deoxyribozymes and Ribozymes

Deoxyribozymes are enzyme-produced, single-stranded DNA molecules designed to attach to the target RNA in accordance with the Watson-Crick base pairing principle. As a result of the RNA cleavage they catalyse, fragments of 2′, 3′-cyclic phosphate and 5′-hydroxyl ends are produced. With the aid of the

cofactors Ca2, Mg2, Pb2, and Zn2, they also facilitate the creation of bonds by ligating the 3′-hydroxyl and 5′-triphosphate terminals of RNA[50][51].

New diagnostic and therapeutic applications have been developed using engineered ribozymes with enhanced substrate recognition domains and catalytic activity. They break RNA at precise cis or trans locations without the need for protein. The Hammerhead ribozyme (HHRz) is an example, found in all species [52].

CRISPR

Long non-coding RNA genes are not susceptible to a few base insertion, deletion, or frameshift mutations like protein-coding genes are. As a result, they might behave via broad frameworks that demand large-scale manipulation. By using the CRISPR/Cas9 technology and paired single guide RNAs (sgRNAs), mice had the maternally expressed lncRNA gene Rian's 23 kb removed. Additionally, the efficiency of the deletions was increased by the use of many sgRNAs, and deletions were also inherited[53][54].

CRISPR interference can sterically suppress the transcription of lncRNA genes (CRISPRi). A guide RNA (gRNA) to identify the target gene and a catalytically dead Cas9 (dCas9) protein with no endonucleolytic activity are both components of CRISPRi. gRNAs specifically target non-template DNA strands in the promoter, template strand sequences, regions that are 100 bp upstream of the promoter, and -35 regions. In eukaryotic cells, this is more efficient than directly inhibiting RNA polymerase[55].

Interfering lncRNA functions

Small molecules

To prevent interactions between them, small compounds either bind to lncRNAs or RNA-binding proteins (RBPs), alter their secondary or tertiary structures, or directly mask RNAs' protein-binding regions or the lncRNA binding domain of RBPs[56].

Aptamers

Single-stranded nucleic acids (DNA/RNA) called aptamers have a high level of target selectivity and affinity. They are, in other words, nucleic acid analogues of antibodies, but they have higher tissue penetration, transport, and immunogenicity. They interfere with RNA-protein interactions, recognise secondary lncRNA structures, and act through three-dimensional structures[57].

Nanobodies

RNA-protein networks associated with cancer can be disturbed by nanobodies. They are a changeable component of highly specific and affine camelid heavy-chain antibodies (HcAbs). Additionally, they resemble the human Immunoglobulin heavy chain V gene (VH) sequences and are very stable and soluble antigen-binding proteins, making them non-immunogenic. They can disrupt RNA-RBP networks that are particular to cancer and interfere with protein-protein or protein-protein interactions[58].

RNA decoy

It is possible to create RNA decoys that mimic lncRNAs and work by attaching to proteins to sequester those proteins. They might serve as a strategy to prevent the formation of useful lncRNA-RBP complexes. An anti-HIV spoof that specifically targets the viral protein Tat been created by scientists. It binds to Tat protein and has a (TAR) RNA hairpin. Unlike natural TAR RNA, which is found in the nucleus, this decoy localises in the nucleolus[59].

CONCLUSION

In cellular physiology, development, and disease states like cancer, long non-coding RNAs play important functions. Consequently, they have a desirable potential for healingcancer therapy objectives and medications. However, there is little history of lncRNA therapeutic targeting. The majority of the delivery methods and targeting tactics have been tested on mRNA and microRNAs. Only one clinical experiment employing lncRNAs has been described (www.clinicaltrials.gov, NCT02641847). It is important to thoroughly investigate the challenges facing the creation of lncRNAs that target therapies. A thorough understanding of the location, structures, functional motifs, methods of action, and interactions of lncRNAs with other biological molecules may be made possible with the aid of bioinformatics, extensive databases, and high-throughput technology. To find suitable lncRNAs as therapeutic targets, a thorough functional screen is necessary. To prevent toxicity and create effective and secure medications, it is also crucial to thoroughly research the specific characteristics of modified oligonucleotides[60].

Model animals should be used to evaluate the expression of human lncRNA, which requires understanding the intricate relationships between lncRNA and its protein and gene targets[61]. LncRNAs are not well preserved between species, though. Few orthologous lncRNAs between humans and mice and several human lncRNAs could not be detected in mice. It may be advantageous to create modified mice models with larger human genome fragments or complete chromosomes, or to swap mouse genome proteins[62].

Although differential lncRNA expression patterns have been documented in some instances, long ncRNAs exhibit tumor-specific expression patterns. A comprehensive investigation of cancer tissue may be more accurate than a bulk tissue assessment because cancer heterogeneity may be causal. A general examination of tumour tissue could result in the loss of a transcript isoform of lncRNAs since lncRNAs are very susceptible to alternative splicing[63].

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