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Long non-coding RNA (LncRNA) as a biomarker and therapeutic agent for cancer

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ABSTRACT

Long non-coding RNA (lncRNA) are transcripts of >200 nucleotides that do not translate into proteins. Once considered as a part of transcriptional noise, now with advanced genome-wide mutation studies it has been shown that lncRNA are involved in various functional and structural aspects of cells. LncRNA plays a crucial role in the regulation of gene expression by regulating chromatin structure and mediates posttranscriptional regulation. LncRNA is involved in the regulation of protein activity and maintains nuclear architecture. Cancer occurs due to the functional disintegration of the intrinsic networking of cells and the formation of a microenvironment for tumour cells. Functional mutation in the noncoding genome with a major effect on lncRNA expression gives rise to most of the cancer. LncRNA are specifically involved in providing cancer phenotypes such as sustained proliferation, enhanced mobility and viability impaired cytostatics etc. LncRNA shows tissue-specific expression and is found circulating in body fluids, are stable there for a long time hence these properties make them suitable biomarkers for diagnosis and prognosis of different cancers. Therapeutic targeting of lncRNA can provide a cure for certain types of cancer. Multiple targeting approaches like knockdown of pathogenic lncRNA by post-transcriptional degradation, modulation of lncRNA gene or inhibiting lncRNA interaction with protein can be used to treat cancer. This review explains how lncRNA regulates genes, how lncRNA acts as a driver of cancer phenotype, how LncRNA can be used as a diagnostic and prognostic biomarker for cancer and finally therapeutic targeting as a cure for cancer in future

KEYWORDS

Biomarker, Cancer, Long Non-Coding RNA (LncRNA), Mutation, Therapeutic Targeting

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Long non-coding RNA are transcripts of length >200 nucleotides, that do not translate into proteins. Most lncRNA in eukaryotes are transcribed by pol II except murine heat shock-induced SINE RNA and many others are produced by RNA polymerase III. Recent studies show two specialized RNA Polymerases Pol IV and Pol V transcribe some lncRNA in plants (Benhamed *et al*., 2015). Many lncRNA are capped at 5′ end except intronic LncRNA and cirRNAs, 3'end of LncRNA may or may not be polyadenylated (Yang *et al*., 2011). LncRNA has slightly longer and fewer exons than protein-coding genes (PCGs).

One of the unique features of LncRNA is the H3K4me1 mark present near the enhancer element (Guttman *et al*., 2009). LncRNA are developmentally and temporally restricted to specific tissues or organs showing that they work in a tissue-specific manner and play a role in specific cellular processes. LncRNA generally does not show conservation across species. LncRNA are localized in both cytosol and nucleus, and they can form secondary structure. As the name suggests they must not code for proteins, but recent research shows that some lncRNA include short open reading frames and undergo translation, but only a few translation products are stable and functional.

Differential hybridization screens of cDNA libraries to clone and study genes were used to discover the first lncRNA, H19 though it was first classified as mRNA. The pioneering studies of Xi and H19 have shown the biological relevance of lncRNA (Loda and Heard, 2019). Recent studies have shown that lncRNA genes are the major component of the genome and contribute to biological activity and various diseases. Understanding the mechanism of action and its role in cancer is main aim of scientists for further consideration of lncRNA in therapeutic and clinical trials. An in-depth analysis of the mechanism of action and further research need to be done to introduce EGFR-AS1 as a biomarker and diagnostic tool (Zhu *et al*., 2023)

Role of Long Non-Coding RNA in Cancer Pathways

LncRNA plays a role in various functional and structural aspects of cells. It has been found that genome-wide cancer mutations are functional mutations within the non-coding genome, with a major effect on lncRNA expression. LncRNA drives cancer through various interactions with RNA, DNA, and proteins, and plays a major role in different signaling pathways lncRNA functions as a mediator of signal transduction in the cancer signaling pathway. The key signaling mediator like protein kinases, transcription factors, and receptors interact with lncRNA and these LncRNA regulate their enzymatic activity.

Cell Signaling Pathways

Cell signaling plays a crucial role in various cellular processes. In response to various intracellular and extracellular stimuli, signaling pathways are critical to several biological reactions and the expression of genes. Some most important cell signaling pathways in cancer include p53, NF-ϰB, p13k/AKT and Notch.

LncRNA and Regulatory Network of p53

P53 is a tumour suppressor, it regulates genes of cell cycle, apoptosis and DNA repair. Mutation or loss of function in p53 can lead to cancer therefore, it is necessary to maintain p53 levels in cells.

Regulation can be done at transcriptional and posttranscriptional levels or by maintaining protein stability. In addition to many protein factors, lncRNA also plays a role in the p53 regulatory network (Zhang *et al*., 2014). Many lncRNA serve as p53 effectors and participate in downstream events in p53-dependent pathways. Some group of lncRNA also regulates p53 expression and stability by an auto-regulatory feedback loop. DINO (Damage induced non-coding) is required for p53-mediated phenotypes like cell cycle arrest, and apoptosis DINO interacts physically with p53 and stabilizes it, which in turn activates various downstream targets including itself (Schmitt and Chang, 2016). LincROR can provide additional mechanisms to the p53 level and can turn down p53 translation. MiR-145 can target lincROR by competing endogenous RNAs mechanism. In this way, miR-145 can help to keep the lincROR level low. LincRNA-P21 functions as a repressor in the p53 pathway. PANDA plays a role in p53-regulated cell cycle, apoptosis. LOC285194 acts as p53 effector and suppresses tumor growth (Zhang *et al*., 2014).

LncRNA also Mediates NF-kB Signaling

NF-ϰB is a ubiquitously expressed pleiotropic transcription factor. It plays a major role in cell growth inflammation and cancer metastasis. Under normal conditions, NF-kB remains in cytoplasm in the form of a complex with 3 subunits p50, p65, and inhibitory IkBα undergoes phosphorylation and degradation. p50 and p56 subunits train the nucleus and regulate the expression of specific target genes. Dysregulation in NF-kB and its target leads to inflammation, drug /radiation resistance and cancer metastasis (Aggarwal, 2004). Numbers of lncRNA affect NF-kB signaling directly or indirectly. However, the main focus is on direct regulation. NF-ϰB interacting lncRNA (NKILA) interacts with NF-kB/IkB complex such that NKILA prevent phosphorylation of IkB by IKK. NKILA can form a heterotrimeric complex which can explain why a low level of NKILA is responsible for breast cancer metastasis and poor prognosis of patients. Lethe is NF-ϰB associated lncRNA which can be induced by NF-kB mediated cytokinase. Lethe repress activities of NF-kB by physical interaction with p65 submit.

HOTAIR decrease IkBα transcription by PRC2 in ovarian cancer, further, HOTAIR can activate NF-kB by cyclic AMP-dependent protein kinase (PKA) and nuclear kinase such as MSK and MASK2. MALAT 1 interacts with p65/p50 heterodimer in such a way that TNFα and IL-6 expression is suppressed (Schmitt and Chang, 2016).

LncRNA Act as AKT Regulators

Many evidence was found in support of the role of AKT in cancer. Growth factors interact with RTK (receptor tyrosine kinase) which generates secondary messenger PIP3 by p13k, which subsequently actives downstream targets of AKT and mTOR. LncRNA AKO23948 is involved directly in AKT pathway (Koirala *et al*., 2017) and it positively regulates AKT. LINK-A (long intergenic non-coding RNA for kinase activation) directly interact with the pleckstrin homology domain of AKT and PIP3 to increase /promote AKT activity. LINKA is necessary for AKT-PIP3 interaction and enzymatic activation subsequently. FER1L4 inhibit the activity of AKT by increasing PTEN expression which is a phosphatase that reverses PIP2 to PIP3.

Notch Signaling Pathway is also associated with lncRNA

The notch signaling pathway is one of the most conserved signaling systems in multicellular organisms and is involved in proliferation differentiation and cell death. LUNAR1 is shown to be regulated by Notch and Notch1 can specifically induce TUG 1 expression which leads to self-renewal of glioma stem cells (Katsushima *et al*., 2016). NALT (notch-associated lncRNA in T cell acute lymphoblastic leukemia 1) is regulated in the bone marrow of T-ALL patients. NALT suppression can impair ectopic NICD expression which promotes cell proliferation or xenograft tumor growth.

LncRNA are the Driver of Cancer Phenotype

Cancer occurs due to dysfunctional intrinsic networking of cells and intercellular communication between tumour cells to generate microenvironment.

Intrinsic networking is disturbed so that proliferation, impaired cytostatic and differentiation signals, enhanced viability and promoted motility can be sustained. LncRNA are specifically involved in providing these phenotypes to a cell (fig 4) (Schmitt and Chang, 2016).

Proliferation Circuits

Androgen signaling also relies on several lncRNA involved in prostate cancer proliferation, PCGEM1, PRNCR1 and HOTAIR directly interact with the androgen receptor to enhance its further signaling and lncRNA CTBP1-AS can interact with an inhibitor of antigen receptor that is CTB1 and increasing androgen response. 8q24 locus amplification is an oncogenic event in most human malignancies resulting in MYC amplification. The role of lncRNA in MYC-driven cancer is shown. PVT1 is a lncRNA gene found at the breakpoint of t (2:3) translocation in Burkitt lymphoma bringing the human immunoglobulin enhancer to PVT1-MYC locus, Myc alone was not sufficient to enhancer tumour formation, whereas multigene segment amplification containing MYC and lncRNA PVT1promote tumour formation (Tseng *et al*., 2014). MYC activation can be activated by CCAT1 lncRNA by providing long-range interaction between MYC and enhancer element (Schmitt and Chang, 2016).

Tumor Suppressor Circuits

LncRNA are also involved in regulating tumor suppressor and growth arrest pathways. The Transcription of lncRNA is regulated under the cell cycle and during senescence (Abdelmohsen *et al*., 2013). The lncRNA MIR31HG recruits polycomb group protein to the INK4A locus which represses its transcription during the normal cell cycle and during senescence MIR31HG is sequestered away from INK4A locus. The lncRNA FAL1 present in chromosome 1, with frequent amplification in cancer, recruits chromatin repressor protein BMI-1 to many genes like CDKN1A which promotes cell proliferation. MEG-3 (Maternally inherited gene 3) is a transcript, it is maternally imprinted. In normal cells, MEG-3 is expressed, and the loss of function of this lncRNA is observed in the majority of meningiomas, and pituitary adenomas (Zhang *et al*., 2010).

Viability Circuits

Tumor cells derive advantage by telomere maintenance, nutrient stress tolerance and maintenance of an undifferentiated state. Gas5 lncRNA (growth arrest specific5) is induced by the withdrawal of growth factors. It blocks the expression of the glucocorticoid-responsive gene by binding to the DNA binding domain of the glucocorticoid receptor and works as decay. This leads to a decrease in cellular inhibitors for apoptosis in normal cells during nutrition stress thereby enhancing apoptosis. But in human breast cancer suppression of Gas5 results in an increase in the viability of breast cancer cells even in a nutrient-poor microenvironment.

The immortality of tumour cells requires the maintenance of telomeres to avoid senescence during replication. Marek's disease virus efficiently induced T cell lymphomas in chicken; the virus expresses a viral telomerase RNA which promotes telomere lengthening. LncRNA can also act as telomerase RNA and can promote telomere lengthening. LncRNA NORAD has shown an effect on chromosome stability. It sequesters the PUMILIO protein away from mRNA involved in mitosis, replication and DNA repair. PUMILIO protein negatively regulates those mRNA and hence decreases mRNA stability and translation, NORAD (K/O) cell hyperactivates PUMLIO and develops genomic instability and aneuploidy. Aneuploidy and chromosome aberration are some of the prominent features of cancer cells. LncRNA is also involved in the maintenance and differentiation of stem cells. Cancer cells can also opt for these features. LncTCF7 a lncRNA recruits SWI/SNF complex to promoter of TCF7 which activates wnt signaling and, in turn, maintains self-renewal of liver cancer stem. The NBAT1 (lncRNA) is also involved in neural differentiation in neuroblastoma cells (Pandey *et al*., 2014).

Motility Circuits

MALAT 1 overexpression predicts a high risk of cancer metastasis in the early stage of non-small cell lung cancer. Many lncRNA have been involved in cancer invasion and metastasis. The lncRNA LET makes the connection between hypoxia response and metastasis.

Hypoxia-induced histone deacetylase 3 suppresses the promoter of LET, resulting in a low level of LET and hence accumulation of NF90 and cells undergo hypoxia-induced cellular invasion.

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