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Long non-coding RNAS: Molecular functions, mechanisms, and clinical implications

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Abstract
Long non-coding RNAs (lncRNAs) have emerged as a major class of regulatory RNA molecules with crucial roles in gene regulation, development, and disease. Although they lack protein-coding potential, lncRNAs account for a significant proportion of the mammalian transcriptome and exhibit remarkable tissue, developmental stage, and cell-type specificity. Advances in large-scale genome and transcriptome projects have overturned the notion of "junk DNA," revealing that lncRNAs participate in diverse biological processes, including chromatin remodeling, transcriptional and post-transcriptional regulation, genomic imprinting, X-chromosome inactivation, and cellular differentiation. This review provides a comprehensive overview of the molecular characteristics, structural features, classification, and functional mechanisms of lncRNAs. Special emphasis is placed on their involvement in normal development, epigenetic regulation, and pathological conditions, particularly cancer. The emerging role of lncRNAs as diagnostic, prognostic, and therapeutic biomarkers is discussed, including their detection in circulating body fluids and their relevance in veterinary oncology such as horn cancer in cattle. Finally, current challenges and future prospects in lncRNA research are highlighted, underscoring their potential as novel targets for epigenetic intervention and precision medicine in both human and animal health.

Keywords: Long non-coding RNA, epigenetic regulation, gene expression, X-chromosome inactivation, genomic imprinting, development, cancer biomarkers, horn cancer, veterinary genomics

Introduction
Large-scale genome projects have revealed that regions once dismissed as "junk DNA" actually perform important regulatory functions. Although the human genome contains only about 20,000 protein-coding genes that is less than 2% of total DNA. This suggests that organismal complexity cannot be explained by protein-coding genes alone and is instead influenced by processes like RNA splicing and post-translational modification. Systematic transcript mapping identified thousands of non-coding RNAs, including ~35,000 non-coding transcripts described by the FANTOM project. These non-coding RNAs are broadly classified as small ncRNAs and long non-coding RNAs (LncRNAs). The small ncRNAs are represented by a broad range of known and newly discovered RNA species, with many being associated with 5' or 3' regions of genes. Whereas, LncRNAs are defined as a heterogeneous group of transcripts ranging in length from 200 nt to ~100 kb, lacking significant Open Reading Frames (ORF), do not exhibit coding potential, transcribed by RNA polymerase II, undergo post-transcriptional processing such as alternative splicing, 5′ capping, polyadenylation, RNA editing and also carry Single Nucleotide Polymorphisms (SNPs) (Jarroux *et al.,* 2017) [9].

The structure of LncRNA
RNA is a very flexible and dynamic molecule that forms complex secondary structures. The structure of LncRNA defines its cellular degradation and its functional versatility, allowing it to set up its subcellular location and form interactions with protein complexes. An increasing number of examples show that the secondary structure of LncRNA constitutes the main primary functional unit, thus bypassing the absence of evolutionary constraints (no code for proteins) and their poor sequence conservation between living species. HOTAIR is the most

studied example, characterized only in mammals, and sharing only 58% homology between mice and men (Bhan and Mandal, 2015) [3], but with a conserved function of epigenetic regulation of chromatin domains.

Characteristics of LncRNAs

LncRNAs are typically characterized by features similar to messenger RNAs, including 5′ capping, 3′ polyadenylation, multiple exons, transcriptional activation and splicing and they are predominantly transcribed by RNA polymerase II. However, unlike mRNAs, they generally lack clear Open Reading Frames (ORFs) and do not always undergo standard mRNA-processing pathways. LncRNAs are widely conserved across a broad range of organisms, including animals, plants, yeast, prokaryotes, and even viruses. It is estimated that up to 80% of transcription in mammalian genomes is associated with LncRNAs. Moreover, LncRNAs exhibit striking biological specificity, showing approximately 78% tissue, developmental-stage and cell-subtype specificity, which is much higher than that observed for mRNAs, where only about 19% demonstrate comparable specificity (Yan *et al*., 2013) [18].

Functions of LncRNA

LncRNAs perform a wide variety of regulatory and cellular functions. They are involved in controlling transcription, splicing and translation and can influence protein localization and the maintenance of cellular structural integrity. LncRNAs also participate in genomic imprinting, regulation of apoptosis, maintenance of stem cell pluripotency and cellular reprogramming. Many LncRNAs play key roles in cancer progression and can act as precursors for small RNAs, including endogenous siRNAs. Because of these diverse activities, LncRNAs are increasingly recognized as important contributors to the development and progression of numerous human and animal diseases.

Classification of LncRNA

Classification methods of LncRNAs according to their different features

1) Genome location and context
2) Exerted effect on DNA sequences
3) Mechanism of functioning and
4) Targeting mechanism (Ma *et al.,* 2013) [14]

1. Based on genomic location & context

a) Intergenic vs intronic: Intergenic long non-coding RNAs (lincRNAs) are located between protein-coding genes and are well-studied; they are often conserved and exhibit tissue-specific expression. In contrast, intronic LncRNAs are transcribed from the introns of protein-coding genes, and relatively few of them have been functionally characterized.

b) Sense vs antisense: Sense LncRNAs are transcribed from the same strand as protein-coding genes and may partially or completely overlap with them. In contrast, antisense LncRNAs are transcribed from the opposite strand and commonly regulate ther paired coding genes.

2. Based on effects on DNA sequences

a) **Cis-acting LncRNAs:** Cis-acting LncRNAs regulate gene expression at genomic loci located in close proximity to their site of transcription. These LncRNAs typically influence neighboring genes through mechanisms such as transcriptional interference, whereby they block or reduce transcriptional activity, or through the recruitment of chromatin-modifying complexes, including Polycomb repressive complex 2 (PRC2), which alter local chromatin structure and thereby modulate gene expression. A well-characterized example of this class is Xist, which functions in cis to initiate X-chromosome inactivation.

b) Trans-acting LncRNAs: Trans-acting LncRNAs regulate genes located at genomic regions distant from the site of their own transcription. Unlike cis-acting LncRNAs, they do not act locally but are often transported to their target loci, where they interact with specific chromatin regulators or transcriptional complexes. Through this recruitment of protein complexes, trans-acting LncRNAs modulate gene expression across different chromosomal locations. A well-known example is HOTAIR, which is transcribed from the HOXC locus but regulates gene expression at the HOXD locus and other distant genomic sites.

3. Based on mechanism of function

a) Transcriptional regulation: Influence gene transcription via transcriptional interference and chromatin remodeling. Examples: Xist, HOTAIR, HOTTIP, COLDAIR.

b) Post-transcriptional regulation: LncRNAs also participate in post-transcriptional regulation, where they influence gene expression after transcription has occurred. These functions commonly involve modulation of mRNA processing events such as splicing, as seen in the case of MIAT, which interacts with splicing factors to alter splice-site selection. In addition, certain LncRNAs regulate translation by interacting with translation initiation factors or ribosomal components, thereby affecting the efficiency of protein synthesis. Examples include BC1 and BC200, which repress translation initiation through binding to translational regulatory proteins.

c) Other functions: Some LncRNAs influence protein localization by directing specific proteins to defined subcellular compartments, while others participate in telomere replication, as exemplified by TERC, which serves as the RNA component of the telomerase complex. LncRNAs also contribute to RNA interference pathways and play important roles in maintaining nuclear organization and structural integrity. These diverse functions highlight the broad regulatory capacity of LncRNAs beyond classical gene expression control.

4. Based on targeting mechanism

Based on their targeting mechanism, LncRNAs can function in several ways. Some act as signals, being expressed under specific conditions, as exemplified by Xist and COLDAIR. Others function as decoys, binding to and sequestering proteins, such as PANDA. Certain LncRNAs serve as guides, directing protein complexes to specific DNA regions, with HOTAIR being a well-known example. Finally, some LncRNAs act as scaffolds, bringing multiple proteins together to form functional complexes, as seen with HOTAIR and 7SL.

Involvement of LncRNA in development

X-chromosome inactivation

In therian mammals, females possess two X chromosomes whereas males have only one, creating the need to balance X-

linked gene expression between the sexes. This balance is achieved through X-Chromosome Inactivation (XCI), a process in which one X chromosome in females becomes transcriptionally silenced (Lyon, 1961) [13]. In placental mammals, XCI occurs as imprinted XCI, where the paternal X chromosome is preferentially silenced in early embryonic and extra-embryonic tissues, and random XCI, in which either the maternal or paternal X chromosome is inactivated in embryonic cells, resulting in mosaic expression patterns in females. The process is regulated by the X-inactivation center (Xic), which encodes several LncRNAs, most notably Xist. Xist is expressed exclusively from the chromosome that will become inactive and spreads along it to form an RNA "coat," thereby recruiting chromatin-modifying complexes such as PRC2 to establish transcriptional silencing.

The regulation of Xist itself involves additional LncRNAs. Tsix, which is transcribed antisense to Xist, represses Xist expression prior to X-chromosome inactivation, thereby helping determine which X chromosome remains active. Conversely, Jpx functions as an activator of Xist in trans by displacing the transcriptional repressor CTCF from the Xist promoter region. Together, these coordinated regulatory mechanisms ensure the correct initiation, spreading and maintenance of X-chromosome inactivation, establishing a classical paradigm for RNA-mediated epigenetic regulation.

Regulation of allelic expression: Genomic imprinting

Genomic imprinting is a form of epigenetic regulation in which certain genes are expressed in a parent-of-origin-specific manner, resulting in monoallelic expression of either the maternal or paternal allele. Similar to X-chromosome inactivation, imprinting is governed by Imprinting Control Regions (ICRs), many of which transcribe LncRNAs that regulate neighboring protein-coding genes. One of the earliest and most abundant embryonic LncRNAs identified was H19, which is reciprocally imprinted with Igf2 and additionally functions as a precursor for several microRNAs. Imprinted genes are essential for fetal growth, metabolic regulation and postnatal behavior, and they typically occur in ~1 Mb clusters controlled by ICRs, where either the maternal or paternal allele is selectively expressed (Barlow, 2011) [1]. Two principal mechanisms operate within these clusters: the insulator model, classically represented by the H19/Igf2 locus, and the more prevalent LncRNA-mediated model, exemplified by the Igf2r/Airn locus. Together, these observations highlight LncRNAs as key regulators of parental allele-specific gene expression and epigenetic inheritance.

Involvement of LncRNAs in normal development

LncRNAs play critical roles in regulating normal development by modulating gene expression programs, particularly within the Hox gene clusters. The LncRNA HOTAIR, transcribed from an intergenic region within the human HOXC cluster, represses genes in the HOXD cluster in trans, thereby influencing the anterior-posterior patterning of the embryo (Rinn *et al*., 2007) [15]. Hox genes encode transcription factors that determine the identity of embryonic segments and the type of structures that form on them, such as vertebrae in humans or legs and wings in fruit flies. During development, Hox gene expression is controlled by LncRNAs through chromatin modifications and changes in chromosome architecture. For example, the LncRNAs Hotdog (Hog) and Twin of Hotdog (Tog), located near the HoxD locus and transcribed from opposite strands, are specifically expressed in the caecum and physically associate with HoxD genes to regulate their expression. Disruption of Hog or Tog expression abolishes HoxD activity in the caecum, demonstrating that these physical LncRNA-gene interactions are essential for proper spatial regulation of HoxD genes during organ development (Delpretti *et al*., 2013) [5].

Homeotic transformation

The long non-coding RNA HOTAIR was the first LncRNA reported to silence genes in trans, particularly the HOXD cluster (Rinn *et al*., 2007) [15]. Knockout of Hotair in mice leads to derepression of multiple target genes, including Hoxd10 and Hoxd11, which are critical for the patterning of the lumbosacral junction and the metacarpal and carpal bones in the limbs. This misregulation contributes to homeotic transformations of the axial skeleton observed in Hotair knockout mice (Li *et al*., 2013) [11]. Genome-wide studies using RNA sequencing and conditional inactivation have shown that Hotair is also required to repress additional HoxD genes as well as several imprinted loci, including Dlk1-Meg3 and Igf2-H19, without altering imprinting choice. Mechanistically, Hotair functions by binding both the PRC2, which catalyzes histone H3 lysine 27 trimethylation (H3K27me3), and the Lsd1 complex, which demethylates histone H3 lysine 4 (H3K4), thereby establishing a repressive chromatin state. Loss of Hotair results in gain of H3K4 trimethylation (H3K4me3) and a partial loss of H3K27me3 at target loci, demonstrating its key role in maintaining transcriptional silencing of Hox and other developmentally important genes (Zhao *et al*., 2010) [20].

Role of LncRNAs in diseases

LncRNAs are RNAs with some special features, such as higher tissue-specificity, higher stage specificity and higher cell subtype specificity, and therefore their expression markers could be used for biomarkers of diagnostics and classification in tumor diseases and tumorigenesis.

LncRNAs biomarkers for tumor prediction

LncRNAs have emerged as promising biomarkers for tumor prediction due to their aberrant expression in various cancers. RNA FISH techniques are increasingly used to detect these changes, with PCA3 and PCAT1 being commonly studied in prostate cancer, GAS5 in breast cancer, and UCA1 is showing downregulation in bladder cancer (Eissa *et al*., 2015) [6]. Exon microarray analyses across thirteen different cancers, including prostate, breast, and bladder cancers, further support the utility of LncRNA detection via FISH (Gupta and Tripathi, 2017) [7]. Given the heterogeneity of cancer, LncRNAs often display subtype-specific expression, such as MIAT in the mesenchymal subtype of ovarian cancer and RMST in rhabdomyosarcoma, highlighting their potential in distinguishing individual tumor subtypes. However, these findings require further validation using RNA FISH and qRT-PCR to confirm subtype-specific expression patterns.

LncRNAs biomarkers for tumor prognosis

According to recent clinical assays, several LncRNAs increase and decrease have been demonstrated in some special tumors. For example, up-expressed HOTAIR, HOTTIP, DANCR and CCAT1 are related with poor survival from colon cancer patients (Luo *et al.,* 2016) [12]. Some LncRNAs such as RP1, RP4, RP11 and RP13 profiles are going to be used to study tumor prognosis with up-expressed and down expression in breast. The oncogenic LncRNA and tumor suppressive LncRNA profiles are discovered to relate with

many tumor diseases, including hepatocellular carcinoma, lung cancer, colorectal cancer, breast cancer, prostate cancer, stomach cancer and glioblastoma.

LncRNAs biomarkers in circulating LncRNA and body liquid

Non-tumor tissue processes are very popular techniques for downstream genomic analysis including LncRNA performance because of their non-invasive process. Non-tumor tissue processes for LncRNA analysis include body liquid specimens, cell free circulating LncRNAs, Circulating Tumor Cell (CTC) and exosome. Clinically, at present, LncRNA begin to be used to study special LncRNA expression in some special tumors and global profiling of the LncRNA aberrance. MALAT-1 was discovered down-regulated in lung cancer from peripheral blood cells while HOTAIR was discovered up-regulated in colon cancer from peripheral blood cells. PCA3 is uncovered in urine of prostate cancer patients while UCA1 is found in urine of bladder cancer.

LncRNAs predicting tumorigenesis

LncRNAs are frequently altered by Somatic Copy-Number Alterations (SCNAs), with about 21.8% of lncRNA genes located in focal SCNA regions. Some of these altered LncRNAs influence cancer development; for example, the amplified LncRNA FAL1 suppresses the tumor-protective gene p21. Because SCNAs can increase or decrease gene expression, LncRNAs within these regions may act as drivers of tumorigenesis, and their expression changes are often linked with cancer (Jeong *et al*., 2016) [10]. However, further confirmation is needed to clearly establish their roles as cancer-causing drivers.

LncRNAs in horn cancer

Horn Cancer (HC) is a common tumor of the horn core epithelium in working cattle, especially castrated bullocks (≈95% of cases), with fewer cases in cows and rare cases in other livestock (Gupta *et al*., 1980) [8]. LncRNAs generally show low expression and high tissue specificity, making them promising prognostic and therapeutic biomarkers (Batista and Chang, 2013) [2]. LncRNAs are already known to play important regulatory roles in bovine development (Yang *et al*., 2018) [19] and their involvement in human cancers has guided research into HC (Chiu *et al*., 2018) [4].

Using Illumina paired-end sequencing, Sabara *et al*. (2019) [16] identified seven upregulated and one downregulated LncRNAs associated with keratin-related and other cancer-linked genes involved in cell growth, invasion, migration, and communication.

Clinical challenge for application

Aberrantly expressed LncRNAs) in tumors offer important opportunities for cancer diagnosis and therapy. Because LncRNAs show highly specific expression patterns and can be detected in body fluids, they have strong potential for accurate clinical diagnostics. However, current applications are limited by uncertainty over whether abnormal LncRNA expression is a cause or consequence of cancer. Although several companies are developing LncRNA-based therapies (Sánchez and Huarte, 2013) [17], major challenges remain. These include limited understanding of how to effectively inhibit LncRNAs with small-molecule drugs, technical barriers to RNAi-based silencing, and risks that targeting LncRNAs might also harm normal cells. Despite these obstacles, expanding knowledge of LncRNA structure and function is expected to advance their clinical use in cancer diagnosis and treatment.

Conclusion

The LncRNAs are a heterogeneous group of transcripts ranging in length from 200 nt to ~100 kb, lacking significant open reading frames, do not exhibit coding potential, transcribed by RNA polymerase II, undergo post-transcriptional processing such as alternative splicing, 5′ capping, polyadenylation, RNA editing and also carry SNPs. The LncRNAs have about 78% tissue-specificity, higher stage specificity and higher cell subtype specificity while mRNAs are only about 19% tissue-specificity, lower stage specificity and lower cell subtype specificity. The structure of LncRNA defines its cellular degradation and its functional versatility, allowing it to set up its subcellular location and form interactions with protein complexes. The LncRNAs can be classified on the basis of genomic location and context, effect exerted on DNA sequence, mechanism of functioning and targeting mechanism. The LncRNA can function as either of the 4 types: as guides, as scaffold, as signals, as decoys. They regulate gene expression by modulating chromatin remodeling, cis and trans gene expression, gene transcription, post-transcriptional regulation, translation, protein trafficking and cellular signaling. The LncRNAs plays significant role in epigenetics *viz*., genomic imprinting, X-chromosome inactivation and normal development process. These LncRNA play significant role in pathogenesis of several complex diseases. The LncRNA can serve as an important biomarker for early detection of disease, or also can serve as a therapeutic target including cancer.

Future prospects

There is a need for large-scale gain-of-function studies to causally demonstrate LncRNA functions. There is a clear need to develop genetic model systems to understand LncRNAs' function *in vivo*. Use of siRNA to target diseases-associated LncRNAs for therapeutic purpose. They can act as novel epigenetic intervention tools for specific sites within the genome. The LncRNAs will provide new answer to old questions of evolution and development.

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