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Differential Perspectives Between miRNA and lncRNA in Light of Biogenesis and Functions: A Review

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ABSTRACT

The central dogma is suggested that deoxyribonucleic acid is translated into ribonucleic acid (RNA) and then into protein. It is considered that 2–3% of the genomic DNA in a functionally active cell, is transcribed to protein-coding RNA. The presence of noncoding transcripts has been neglected many a time as cellular DNA and transcript noises, however, increasing proof proposes that a very important part of these non-coding transcripts is functionally effective as RNA molecules. The non-coding transcripts of up to 100 bases are known as small non-coding RNA that comprises tRNA, miRNA, snoRNA, piwi-interacting RNA (pi-RNA), etc. Interestingly, rRNA features about 6.9 kb, though these are not considered long-non-coding RNAs. However, RNA molecules that are over 200 bases long (ranging between 0.8 to 10 kb) are known as long non-coding RNA (lncRNA). It does not have open reading frames (with some exceptions), 3`- untranslated regions (3'-UTRs), and these RNAs are devoid of any translation-termination regions. However, these may be capped, spliced, and polyadenylated as RNA molecules and play a major role in factor regulation, neoplastic cell invasion, chromatin granule transforming, and cell differentiation. Downregulation of lncRNA is responsible for numerous diseases in mammals. miRNAs are mature transcripts of 22 nt in length and function as antisense regulators of other RNAs. They play role in post-transcriptional factors and are involved in differentiation, proliferation, immune response, cell growth, and caspase-mediated cell death. Downregulation in miRNA expression has a necessary role in many diseases, together with cancers.

Keywords: Biological Implications, lncRNAs, miRNA.

1 Introduction

Recent advances in understanding biological processes such as growth and development have widely exposed the importance of non-coding RNA (ncRNA) molecules, which serve critical gene regulatory tasks. Aside from the structural role of non-protein-coding RNA (ncRNA) like tRNA and rRNA, various other long and small RNAs have been shown to influence gene regulation both indirectly and directly. ncRNA controls mono-allelic manifestations such as genomic imprinting, X-chromosome inactivation, and allelic exclusion (Achawanantakun et.al, 2015). LncRNAs can interfere with chromatin function, influence immune cell development and function, modify the stability and translation of cytoplasmic mRNAs, and disrupt signaling pathways and their interactions with DNA, RNA, and proteins (Statello et.al, 2020). Many of these roles eventually contribute to gene expression in a variety of biological and physical conditions, such as neurological disorders, immunology responses, and cancer. Long ncRNA area affects genome-wide rearrangements during ciliate differentiation (Ahmed et.al, 2013) and T-cell receptor recombination (Ariel et.al, 2000). Many of these functions contribute to gene expression in a variety of biological and physical diseases, including neurological disorders, immune responses, and cancer. Long ncRNA areas influence genome-wide rearrangements during ciliate development and T-cell receptor recombination (Ahmed et.al, 2013; Ariel et.al, 2000).

The small non-coding RNA is the second type of ncRNA. Small nuclear RNA (snRNA), microRNA (miRNA), small nucleolar RNA (snoRNA), piwi interacting RNA (piRNA), and small interfering RNA (siRNA) are the major groups (siRNA). Other variants of these short RNAs have been found in conjunction with specialized genomic contexts containing comparable repetitions (repeat-associated siRNA or rasiRNA, small Cajal-body specific RNA or scaRNA, trans-acting siRNA). MicroRNAs (miRNAs) are epigenetically modulated gene transcription and have emerged as one of the most widely studied substrates for the creation of liquid biopsy biomarkers for cancer patients (Toden & Goel, 2022).

The advancement of high-throughput sequencing technologies has enabled the comprehensive molecular patient characterization of diverse noncoding RNA expression profiles in a wide range of malignancies. Furthermore, advances in technology for quantifying lowly expressed in circulation have allowed for the robust identification of previously unknown and undetectable biomarkers in cancer patients. Table 1 summarises the major roles of these small ncRNAs. Researchers have been attempting to investigate the numerous non-coding RNAs in human, mouse, and other species systems biology. The current review seeks to outline the biogenesis of miRNAs and lncRNAs, as well as their multifaceted role in various biological processes such as regulation of normal cellular functioning and disease regulation.

Table 1: *Major classes of small non-coding RNA and their biological role*

S. No	Type of small RNA	Abbreviation	Length	Major Functions	Reference
1	Small nucleolar RNA	snoRNA	35nt	Guides chemical modification in rRNA, tRNA, etc	(Bachellerie et.al, 2002)
2	Small nuclear RNA	snRNA	100nt	Splicing, transcription regulation	(Wolff et.al, 1994)
3	Small interfering RNA	siRNA	20-25nt	Post-transcriptional mRNA degradation	(Hüttenhofer et.al, 2002)
4	microRNA	miRNA	17-25nt	Post-transcriptional mRNA degradation / silencing	(Lai, 2003)
5	Piwi interacting RNA	piRNA	26-30nt	Silencing of retrotransposons in germline	(Girard et.al, 2006)
6	Repeat associated siRNA	siRNA	24-29nt	Heterochromatin packaging silencing genes	(Klenov et.al, 2007)
7	Trans-acting siRNA	siRNA	21-22nt	Post-transcriptional silencing, in plants	(Yoshikawa et.al, 2005)
8	Small Cajal-body specific RNA	scaRNA	35nt	Guides chemical modification of spliceosomal RNAs	(Staněk & Neugebauer, 2006)

2 MicroRNA

MicroRNAs (miRNAs) are small non-coding RNAs that are 21-24 nucleotide long and play an important role in post-transcriptional gene regulation. They are also involved in cellular growth, proliferation, differentiation, immunological response, and apoptosis. Lin-4 and let-7 were the first miRNAs found in the worm C. elegans. It has been demonstrated that they regulate the expression of potential. Lin-14 and other complementary mRNAs (W. Chen et.al, 1997; Cho et.al, 2011).Circulating miRNA levels, particularly miR-371a-3p, have the potential to be used in clinical practice and may aid clinical decision-making in a variety of germ-cell tumour circumstances (Leão et.al, 2021). Another study (Cimmino et.al, 2005) discovered that small RNAs of 21-23 nucleotides (now known as miRNA) were formed from both the sense and antisense strands and were complementary to the silenced mRNA. MicroRNAs are important epigenetic factors that regulate bone growth, homeostasis, and repair. They have critical roles in the regulation of skeletal development (Hensley & McAlinden, 2021).

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3 Biogenesis and functions of miRNAs

RNA polymerase II (RNAPII) recognizes most miRNAs as 5' capped, 3' polyadenylated long primary transcripts (pri-miRNA) with many stems or hairpin structures. The RNase III enzyme DROSHA then forms a complex with other proteins, such as DGCR8 (Di George Syndrome Critical Region 8) in mammals and cleaves the pri-miRNA into approximately 60-70nucleotide-longg pre-miRNA, which is then transported into the cytoplasm via the EXP- 5 (Exportin-5) nuclear transport receptor in cooperation with the Ran GTPase co-factor (Lund et.al, 2004; Yi et.al, 2003).

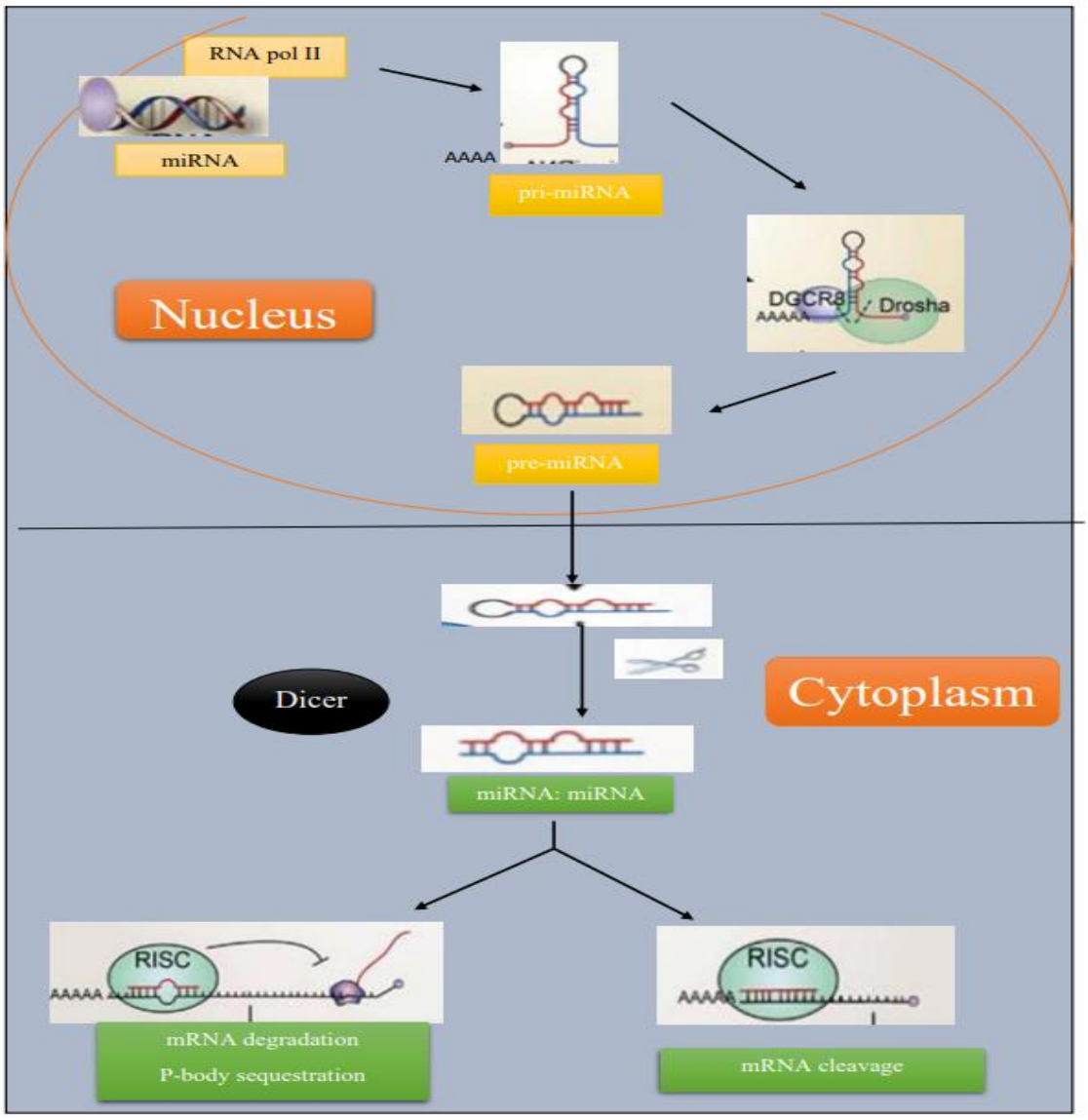

Figure 1: *miRNA biogenesis and function. miRNA genes are transcribed by RNA pol II into primary miRNA transcripts pri-miRNAs which contain a hairpin structure. The hairpin structure is cleaved by the endonuclease Drosha (or Dcl1) to form pre-miRNA which is exported into the cytoplasm and subsequently processed by Dicer into 22-23 nucleotides miRNA duplexes. One strand of the duplex is then incorporated into RISC and guides the complex to its target to facilitate either the target mRNA translational repression or cleavage.*

IPre-miRNA is cleaved in the cytoplasm by DICER, another RNase III-like enzyme, in complex with another protein TRBP (the human immunodeficiency virus Trans activating Response RNA-Binding Protein), resulting in a small RNA duplex with 21-14 nucleotides with 2 nucleotides 3' overhangs on both strands (MacRae et.al, 2006; Saito et.al, 2005). Any of the two strands is loaded into Argonaute (AGO) family proteins (often AGO 2) and combined with an RNA-induced silencing complex (RISC), which works

as a guide strand or matures miRNA, and the other strand is known as miRNA or passenger, which is normally degraded. The stability of a double-stranded RNA's 5'end influences the choice of a guide strand (Fig:1).Mature miRNA is employed as a guide in the RISC complex to recognizee its target mRNA (messenger RNA).In humans, mature miRNA targets the 3' untranslated region (UTR) of mRNA via Watson-Crick base pairing and partially represses the expression of target mRNA via sequence complementarity (perfect or near-perfect complementarity) of the seed region (nucleotides 2 to 8). According to some reports, mature miRNA can also bind to the open reading frame (ORF) or 5'UTR of target mRNA.

Many miRNAs in plants have been found via direct cloning, genetic techniques, and bioinformatic approaches. Plant miRNAs are mostly found in genomic regions that are regulated by their promoter and transcribed by RNA polymerase II (Jones-Rhoades & Bartel, 2004). As a result, it appears that pri-miRNAs are spliced, polyadenylated, and capped during maturation. The Dicer-like proteins termed DCL1, which are homologous to the animal DICER proteins, play an important role in the maturation of miRNAs in plants.

4 Role of microRNAs in disease regulation

It has been observed that miRNA has an important role in human diseases such as viral infections, cancer, and neurological diseases. MiRNAs have critical roles in biological processes such as cell division and death(Ng & Stanton, 2013), intracellular signaling, cellular metabolism, cell mobility, immunity, and so on. miR15 and miR16 were found to be downregulated in patients with B-cell chronic lymphocytic leukemia (B-Cell) (Calin et.al, 2002). Numerous expression profiling studies have found associations between abnormal miRNA expression patterns and higher risk of various types of cancers such as breast cancer due to dysregulation of miR-145, miR-125b, miR-155, and miR-21 expression (Iorio et.al, 2005). A variety of human cancers, including Hepatocellular carcinoma cells and tissues, have been found to have altered miRNA expression in cancer-associated genomic regions or fragile sites. The specific patterns of aberrant miRNA expression vary according to disease ethology, which includes viral hepatitis, alcoholic liver disease, and non-alcoholic steatohepatitis, among many other causes of hepatocarcinogenesis (Morishita et.al, 2021). Furthermore, evidence connected the up-regulation of miR-155 and down-regulation of let-7a with poor lung cancer patient survival (Cho et.al, 2011; W. Kong et.al, 2010), and miR-16, miR-15, and let-7 miRNAs are tumor suppressors, but miR-155 and miR-21 are oncogenes (Calin et.al, 2002; Cimmino et.al, 2005). However, miR-29b and miR-7 play important roles in suppressing liver cancer metastasis via inhibiting PIK3CD and MMP-2 (Fang et.al, 2011). Recent studies found miRNAs that play important roles in neurodegenerative diseases (ND), such as miR-30b, miR-30c, and miR-26a (Martins et.al, 2011), in Parkinson's disease (PD) patients' peripheral blood mononuclear cells. These miRNAs were linked to Parkinson's disease (PD) vulnerability, while the expression of miR-9, miR-29b-1, and miR-29a was considerably reduced in Alzheimer's disease (AD). Another study discovered that miR-326, miR-155, and miR-34a were upregulated in MS lesions (Junker et.al, 2009).

Epstein Bar Virus (EBV) downregulates CXC-chemokine ligand 11 (CXCL11), interferon (IFN)-inducible T-cell chemoattractant, via miR-BHRF1-3 (Xia et.al, 2008). Surprisingly, EBV can increase the expression of cellular miR-155 (Gatto et.al, 2008). These are some intriguing findings illustrating the significance of miRNAs in disease regulation, and they pave the way for additional research to uncover the widespread role of miRNAs in cellular pathogenesis. It was recently discovered that SARS-CoV-2 infection requires both host and viral-encoded miRNAs. Dysregulation of miRNAs, which regulate numerous genes expressed in COVID-19 patients with comorbidities, may modify disease severity.

5 Tools for miRNA structure and function prediction

Each miRNA sequence requires miRNA gene loci, alternative miRNA annotation information, and a data storage platform for pre-miRNA secondary structure (Chen et.al, 2019). miRBase is the most important repository for miRNA storage, containing all known miRNA sequences and annotations for all species.

mirSTP is a database used to investigate miRNA transcription start sites (TSSs). MetaMirClust provided data on miRNA clusters and their conservation. Free energy and structural components are crucial features for computing miRNA molecules in machine learning approach (Lorenz et.al, 2011). ViennaRNA and RNA structure are techniques for predicting the precise structure of miRNAs (Ahmed et.al, 2013). Because the machinery of Dicer cleavage site range is still unclear, techniques like PHDcleav and LBSizeCleav Support Vector Machine (SVM) model are used to determine these sites in pre-miRNAs. The AGO protein family is a key component of the RISC and plays an important role in miRNA targeting. Several tools, like as Antar, miRBShunter, and miRTar2GO, have been developed to observe miRNA-binding sites from AGO-CLIP- (e.g., AGO-PARCLIP and AGO-HITS-CLIP) data. Popular miRNA target prediction software is listed in Table 2.

Table 2: *Popular miRNA target prediction software and their description*

S.No	Software	Description of software	Reference
1.	Miranda	Miranda executes a Dynamic Programming local alignment among the reference sequence and query miRNA sequence through G: U wobble for generating scores for the alignments. ViennaRNA package calculates the thermodynamic stability of the high scoring pairs. Allow comparison of miRNAs complementarity to 3'UTR regions.	(John et.al, 2004)
2.	RNAhybrid	RNAhybrid recognizes domains probable to form RNA duplexes and calculates the minimum free energy (MFE) hybridization of a long and a short RNA.	(Krüger & Rehmsmeier, 2006)
3.	MicroInspector	MicroInspector analyzes user-defined RNA sequence, which is typically an mRNA or a part of an mRNA, for the occurrence of binding sites for known and registered miRNAs and utilizes the principles of nucleotide complementarity. The software also incorporates a dynamic folding algorithm together with a 2D structure analysis that rejects pairs that do not fit in known rules of miRNA–mRNA duplex formation.	(Rusinov et.al, 2005)
4.	DIANAMicro T	DIANA-microT is a web server that provides information for predicted miRNA: target gene interactions with a user-friendly interface, providing extensive connectivity to online biological resources.	(Kiriakidou et.al, 2004)
5.	TargetScan	It is a classical software for miRNA target prediction. The server allows to predict targets of miRNAs by searching for the existence of conserved 7mer and 8mer 'seed' sites that are complementary to the specified miRNA sequences.	(Lewis et.al, 2005)
6.	PicTar	PicTar is a computational method for identifying common targets of microRNAs. It calculates the maximum likelihood score that the sequence is bound by single or combinations of microRNAs.	(Krek et.al, 2005)
7.	miRSVR	Predicts the expected down-regulation of the target mRNA. miRSVR algorithm based on dynamic programming to score a 3' UTR-miRNA duplex created on maximum complementary alignment. miRSVR analysis shows that some targets with non-conserved, imperfect complementary seed matches are functional as they were significantly down-regulated in miRNA transfection assays.	(Betel et.al, 2010)
8.	TarBase	Tarbase is a database of experimentally validated microRNA-mRNA targets. Provides for the first time hundreds of thousands of high-quality manually curated experimentally validated miRNA: gene interactions, enhanced with detailed meta-data. This version of the database is also related to other databases like Swiss-Prot, Ensembl, Hugo, and HGNC to spread evidence about miRNAs and their target mRNAs.	(Papadopoulos et.al, 2009; Sethupathy et.al, 2006)

6 Long-noncoding RNA

The majority of the noncoding genome is made up of housekeeping noncoding RNAs like tRNA and rRNA, as well as small non-coding RNAs like miRNA, snoRNA, siRNA, and piRNA. However, a larger portion of the genome is transcribed into longer transcripts, often greater than 200 nucleotides in length, that resemble mRNAs but lack protein-coding ability (Mercer et.al, 2009). Although their coding potential

is less than 100 amino acids, lncRNAs have a length of more than 2 Kb. They are spliced, polyadenylated, and have a hallmark of cell type-specific expression (Dinger et.al, 2008). By interfering with molecular pathways, lncRNAs regulate the cell cycle, maintain pluripotency, and may potentially play a role in renewal and differentiation throughout organogenesis (Aich & Chakraborty, 2020). Thousands of novel lncRNAs have recently been discovered in various fields of biology, based on secondary structure, tertiary structure, sequencing, or a combination of these. In recent years, sequencing initiatives such as FANTOM and ENCODE have revealed a large number of such noncoding transcripts (Carninci et.al, 2005).

7 Biogenesis and function

The enzyme RNA-polymerase II transcribes lncRNA from exonic, intergenic, or proximal protein-coding regions of the genome (Fig 2). The pre-mature lncRNA is then 3'-polyadenylated and 5'-capped along methyl-guanosine (Losko et.al, 2016). It frequently undergoes alternative splicing, which is necessary for protein diversity.LncRNAs interact with certain splicing factors and subsequently create RNA-RNA duplexes with pre-mRNA molecules, which alter chromatin remodeling and so complete target gene splicing (Romero-Barrios et.al, 2018). For example, LINC-HELLP, a 205 kb-lncRNA, is thought to be important in splicing control and pregnancy-related disease. Purification and mass spectrometry investigations revealed that splicing components (splicing-related factors Y-box Binding Protein 1 (YBX1) and Poly (RC) Binding Proteins 1 and 2) identify this lncRNA, and thus the ribosomal machinery.

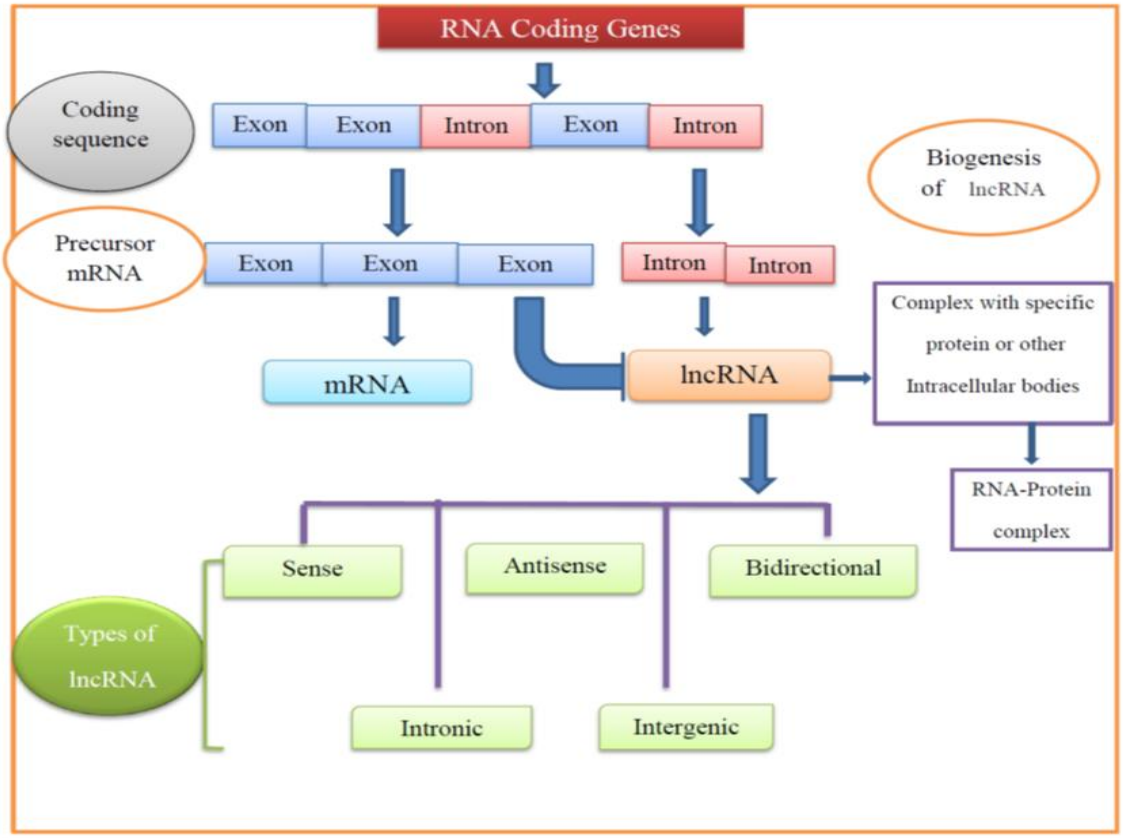

Figure 2: *Biogenesis and classification of lncRNAs in humans and other animals*

So far, the molecular mechanisms of this lncRNA's splicing control are unknown, but due to mutations in patients, some region (5'-end up to the centre) of the LINC-HELLP transcript loses its ability to cooperate with its protein partners. Mutations, on the other hand, increase binding at the 3' end. There is the omission of functional lncRNA that aren't polyadenylated viz. antisense, as-Oct4-pg5' and brain associated 'BC200'

(W. Chen et.al, 1997) lncRNA-encoding genes contain their promoters and have their transcription factors (TFs) and single DNA motifs.

Epigenetic changes influence lncRNA biogenesis. Histone methylation is crucial in transcriptional control. The methylation of histone H3 lysine 4 (H3K4) indicates transcription activation, whereas H3K27 trimethylation indicates gene silence. Several lncRNAs, such as FIRRE, XIST, HOTTIP, and others, play important roles in an organization of 3D nuclear architecture and transcriptional gene activation, while lncRNA decoys, such as lncRNA-DNA triplex or Alu transcripts, can block transcriptional regulation by binding to RNA polII (Mariner et.al, 2008).The binding of distant transcription factors (TFs) to lncRNA results in the formation of a nascent transcript that regulates mRNA processing via alternative splicing. The binding of lncRNAs to mRNA can either prevent or promote translation, as well as facilitate mRNA degradation. Small RNA sequencing (sRNA-Seq) data have showed that lncRNA can also encode small functional RNA. Mature lncRNAs may be found in the nucleus or the cytoplasm. The cytoplasmic lncRNAs are not translated (Guttman et.al, 2013), although small peptides produced by lncRNAs in conjunction with ribosomes have been studied. Because lncRNAs are cell-type specific in their production and expression, they could serve as helpful markers as well as therapeutic targets (Grillone et.al, 2020).

8 LncRNAs in diseases

lncRNA expression patterns are known to be disturbed in a variety of human diseases, including cancer. The bulk of cancer-related single-nucleotide polymorphisms/variations (SNP/SNV) locations are found outside of protein-coding sections of the genome, in introns or intergenic regions. Some of them have been related to known long noncoding RNA (lncRNA) locations. Recently, a few instances of functional lncRNAs transcribed from cancer risk loci, such as SNP rs944289 in the 14q13.3 region, which is associated with papillary thyroid carcinoma (PTC), have been identified (Jendrzejewski et.al, 2012). PTC susceptibility candidate 3 (PTCSC3), a thyroid-specific lncRNA, was discovered to be actively downregulated in papillary thyroid cancer, and the repression was driven by the related SNP. Long noncoding RNAs (lncRNAs) have emerged as critical regulators of cellular activities such as homeostasis as well as disease initiation and progression. Because of their cell, tissue, and disease-specific expression patterns, LncRNAs are therapeutic targets (Pierce et.al, 2022). LncRNAs are commonly targeted by oligonucleotide treatments and developments in oligonucleotide chemistry, such as C2 ribose sugar modifications like 2'-fluoro, 2'-O-methyl, and 2-O-methoxyethyl; 2'4'-restricted nucleotides like locked nucleic acids and constrained 2'-O-ethyl (cEt) nucleotide.

In comparison to normal breast tissue, HOTAIR lncRNA is substantially overexpressed in metastatic breast cancer tissue (Bhan et.al, 2013; Gupta et.al, 2010; Wang et.al, 2013).HOAIR has been implicated in hepatocellular carcinoma, colorectal carcinoma, and gastric carcinoma (Geng et.al, 2011), and it has been discovered to be a negative biomarker of pancreatic cancer, cervical cancer, lung cancer, and esophageal carcinoma (Lv et.al, 2013). MALAT1 (Metastasis Associated Lung Adenocarcinoma Transcript) was identified as a predictive marker of metastasis development in early-stage lung adenocarcinoma (Ji et.al, 2003) and its high expression revealed to be a marker of poor postoperative prognosis in colorectal carcinoma (Ji et.al, 2003; Zheng et.al, 2014). High levels of H19 are caused by a lack of imprinting at the H19 gene in the paternal allele, resulting in biallelic expression in a variety of malignancies (Ariel et.al, 2000). A number of risk factors, including carcinogen exposure, hypoxia, and smoking (Matouk et.al, 2007), have been linked to increased H19 expression. GAS5 is a tumour suppressor lncRNA that suppresses metabolism and growth while also exposing cells to apoptosis by inhibiting glucocorticoid receptors. GAS5 is down-regulated in several cancers such as breast cancer and gastric cancer (Mourtada-Maarabouni et.al, 2008; M. Sun et.al, 2014). Another prominent tumour suppressor lncRNA is Maternally expressed gene 3 (MEG3) which acts by rising p53 activity on specific transcription targets. MEG3 was formed to be downregulated in myeloid leukaemia, meningioma, pituitary adenoma (Benetatos et.al, 2010; Gejman et.al, 2008).

9 Long non-coding RNAs platforms and databases

There are numerous online data sites that provide information regarding lncRNA sequences, the RNA-interactome, and functional annotations. Some contain experimental output data or personally curated data from the literature, while others provide data obtained by in silico prediction. Table 3 lists the data sources containing lncRNA interactomes and annotations, while Table 4 lists the computational strategies for identifying and functionally annotating lncRNAs.

Table 3: *Datasources containing lncRNA interactome and annotation.*

S.No	Source name	Type of Data	Reference
1.	Gencode	A comprehensive database consisting of all gene features in the human and mouse genomes with high accuracy based on biological evidence, and to release these annotations for the advantage of biomedical research and genome interpretation.	(Harrow et.al, 2006)
2.	FANTOM5 CAGE	FANTOM5 CAGE data was performed on the collection of multiple transcripts to generate a comprehensive atlas of human lncRNA genes for the analysis of gene expression data with high-confidence 5' ends and expression profiles from the major human primary cell types and tissues.	(Hon et.al, 2017)
3.	RNAcentral	Combined with multiple expert databases, up-to-date lncRNAs currently covcover species and diverse RNA types. LncRNA significant databases comprised are LNCipedia, LncBase, ncRNAdb, LncBook, and NONCODE.	(The RNAcentral Consortium, 2019)
4.	lncBook	It is a comprehensive lncRNA online analytics platform that features a broad assembly of human lncRNAs and systematic curation by data incorporation, functional annotation, and disease association.	(Ma et.al, 2019)
5.	RISE	It contains data from literature and data sources for mouse, human, and yeast transcriptome and RNA- RNA interactions acquired from experimental sequencing data.	(Gong et.al, 2018)

Table 4: *Computational techniques for LncRNA Identification and functional annotation*

S.No	Tool	Feature set	Reference
1.	CPC	Coding Potential Calculator (CPC) assesses the protein-coding potential of a transcript based on ORF coverage, log-odds score, and ORF integrity. BLASTX: frame score, HSPs (High-scoring Segment Pairs), hit score.	(Kong et.al, 2007)
2.	CPAT	Coding Potential Assessment Tool (CPAT), rapidly identifies coding and noncoding transcripts from a large pool of candidates based on ORF coverage, size, hexamer usage bias, and Fickett TESTCODE statistic.	(Wang et.al, 2013)
3.	PLEK	PLEK (predictor of long non-coding RNAs and messager RNAs based on the k-mer scheme) based on k-mer frequencies of the transcript sequence.	(Li et.al, 2014)
4.	lncR Scan SVM	lncRScan-SVM identifies protein-coding ones and lncRNA transcripts based on their transcript length, CDS score, exon count and length, stop codon standard deviation using a support vector machine (SVM)	(Sun et.al, 2015)
5.	Lnc RNA ID	lncRNA identification tool, distinguish lncRNAs from protein-coding genes based on ORF length, coverage, ribosome coverage on the transcript, ORF, and 3' UTR, uses hidden Markov model (profile HMM)-based alignments.	(Achawanantakun et.al, 2015)
6.	Lnc Score	Provide the information about GC-content, Exon: Hexamer Score (HS), Distance, Fickett Score ORF: Length and Coverage, Coding Score Percentage.	(J. Zhao et.al, 2016)
7.	Lnc Finder	LncFinder can disclose the properties of lncRNA and mRNA from numerous perspectives and lncRNA–protein interaction prediction and analysis of lncRNA evolution based on Sequence Intrinsic Composition like Logarithm-distance of hexamer on ORF, Length, and coverage of the longest ORF, Minimum free energy	(Han et.al, 2019)

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10 Non-coding RNAs as biomarkers

When compared to protein-coding mRNAs in eukaryotic cells, ncRNAs are inert molecules expressed in large volumes. Indeed, ncRNAs have the ability to turn off/reduce the expression of several targets at the same time, impacting entire signalling pathways within cells. Several short noncoding RNAs (ncRNAs) play a role in regulating the expression of genes involved in the development of organ systems such as blood vessels and blood cells (Small & Olson, 2011).Piwi-interacting RNAs (piRNAs), small nucleolar RNA (snoRNA), short interfering RNAs (siRNA), and microRNAs (miRNAs) are examples of regulatory small ncRNAs (Y. Zhao & Srivastava, 2007).Among these miRNAs, ncRNAs have been discovered to be essential for an organism's correct functioning and development (Wienholds & Plasterk, 2005; Y. Zhao & Srivastava, 2007). Several research have been conducted to better understand the function of miRNAs and their role in regulating biological processes such as embryonic development, epithelial to mesenchymal transition, apoptosis, and so on (Garzon et.al, 2010).Deregulation of miRNA expression levels, among other things, contributes to the development of numerous disorders such as cardiac muscle hypertrophy, cancer, and metastasis (Garzon et.al, 2010; Garzon & Croce, 2008). Unlike miRNAs, lncRNAs are tissue-specific and should regulate gene expression at several levels such as transcriptional, post-transcriptional, and epigenetic, as well as creating short-ncRNAs, tiny interfering RNAs, and acting as a scaffold to form ribonucleoprotein complexes. This broad range of functions is attributed to lncRNAs' unique capacity to directly interact with other macromolecules such as RNA, DNA, and protein. Recently, it has been discovered that lncRNAs play an important role in carcinogenesis and thus in the metastatic process.

Furthermore, ncRNAs work as direct/indirect modulators of gene expression, preserving their ability to achieve mRNA target(s) of distinct tissues and circulate stably throughout body fluids (Fanelli et.al, 2018).Extracellular stability and persistence with their various subtypes appear to be stable by themselves (i.e., miRNAs), or molecular alterations like adenylation, methylation, capping, or transportation in extracellular vesicles to block their degradation (i.e., lncRNAs) may be useful characteristics of ncRNAs for clinical purposes. The ability of ncRNA molecules to circulate within body fluids allows them to be used as I next-generation biomarkers of disease, with a significant impact on prognosis, diagnosis, and therapy efficacy evaluation; and (ii) new type of treatment, which may be able to re-establish physiological conditions when ncRNA profiling results dysregulate.

11 Future research perspectives

As the Human Genome Project's discoveries diverge the clinical research landscape, they are contributing to new potential in health problems for producing miRNA treatments that are intangible to existing therapy approaches. According to recent study, non-coding RNAs (ncRNAs) are emerging as key regulators of macro-autophagy in a variety of physiological and pathological processes. According to evidence, macrophage, a highly conserved process involving cellular resources, components, and organelle recycling, can be selective or non-selective, and ncRNAs regulate both selective and non-selective autophagy (Lin et.al, 2022). Long coding RNAs (lncRNAs) and microRNAs (miRNAs) both play key roles in bone marrow function. Changes in the expression levels of miRNAs and lncRNA cause muscular atrophy and sarcopenia through changing numerous signalling pathways (Lee & Kang, 2022). The development of bioinformatic tools for identifying miRNA-binding sites in target genes and their analogues has aided in miRNA translation into clinical treatment. The first siRNA human trials were conducted between 2004 and 2018, and the siRNA treatment was approved (Ozcan et.al, 2015), around 15 years ago. miRNAs maintain good tissue stability, ensuring disease indicators. The construction of their specialised detection method is accessible to the classification of small molecule RNA so that they can be employed in the accurate and logical treatment of disorders. Because a single detection strategy cannot provide accurate and timely detection, detection methods are often integrated and efficiently exploited by combining previous detection strategies. The future of microRNA detection efficiency tends to be united with the biological properties of the principle, which deals with the detection process employing statistical methods limited to conventional detection systems. The majority of

lncRNAs are unknown; some are cytoplasmic, others are nuclear, and some are highly expressed or detectable, and no conservation, stability, or expression level criteria have been identified. For example, Kcnq1ot1 has a half-life of 1 hour (Clark et.al, 2012), lncRNAs Xic are found mainly in placental mammals and have less conservation even in this taxon (Davidow et.al, 2007), and RepA remains at 5-10 copies per cell (J. Zhao et.al, 2008).Evidence suggests that lncRNAs play a role in a variety of biological processes, including the emergence and evolution of malignancies. Furthermore, several lncRNAs were regulated by the m6A modification, which is significantly involved in DNA repair. The increasing roles of lncRNAs in the evolution of human cancers are diverse, as are the processes of lncRNAs in carcinogenesis. More study is needed to demonstrate the link between lncRNAs and cancer. Finally, variations in the expression patterns of some specific lncRNAs can be indicative of malignancy. lncRNAs have the potential to be promising diagnostic biomarkers for cancer detection and can be used to predict cancer patients' future diagnoses.

12 Conclusion

Finally, in this review, we examined the current level of knowledge about the interaction of lncRNAs and miRNAs. In vivo studies are beginning to confirm the biological significance of lncRNAs. Because of the numerous molecular functions of lncRNAs, the majority of which are currently unknown, we can expect lncRNAs to have a stronger impact on cell differentiation. Specifically, lncRNAs and miRNAs carry out biological functions by constructing a huge and complex regulatory network of reciprocal interactions that modulates gene expression.

13 Declarations

13.1 Acknowledgments

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13.2 Conflict of Interest

The authors declare that there is no conflict of interest regarding the manuscript.

13.3 Authors Contribution

All authors have contributed equally during the manuscript preparation.

13.4 Publisher's Note

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References

Achawanantakun, R., Chen, J., Sun, Y., & Zhang, Y. (2015). LncRNA-ID: Long non-coding RNA IDentification using balanced random forests. *Bioinformatics*, *31*(24), 3897–3905. https://doi.org/10.1093/BIOINFORMATICS/BTV480

Ahmed, F., Kaundal, R., & Raghava, G. P. S. (2013). PHDcleav: A SVM based method for predicting human Dicer cleavage sites using sequence and secondary structure of miRNA precursors. *BMC Bioinformatics*, *14*(14), 1–11. https://doi.org/10.1186/1471-2105-14-S14-S9

Aich, M., & Chakraborty, D. (2020). Role of lncRNAs in stem cell maintenance and differentiation. *Current Topics in Developmental Biology*, *138*, 73–112. https://doi.org/10.1016/BS.CTDB.2019.11.003

Ariel, I., Tykocinski, M. L., De Groot, N., Hochberg, A., Sughayer, M., Fellig, Y., Pizov, G., Ayesh, S., Podeh, D., Libdeh, B. A., Levy, C., & Birman, T. (2000). The imprinted H19 gene is a marker of early recurrence in human bladder carcinoma. *Molecular Pathology* , *53*(6), 320–323. https://doi.org/10.1136/MP.53.6.320

Bachellerie, J. P., Cavaillé, J., & Hüttenhofer, A. (2002). The expanding snoRNA world. *Biochimie*, *84*(8), 775–790. https://doi.org/10.1016/S0300-9084(02)01402-5

Benetatos, L., Hatzimichael, E., Dasoula, A., Dranitsaris, G., Tsiara, S., Syrrou, M., Georgiou, I., & Bourantas, K. L. (2010). CpG methylation analysis of the MEG3 and SNRPN imprinted genes in acute myeloid leukemia and myelodysplastic syndromes. *Leukemia Research*, *34*(2), 148–153. https://doi.org/10.1016/J.LEUKRES.2009.06.019

Betel, D., Koppal, A., Agius, P., Sander, C., & Leslie, C. (2010). Comprehensive modeling of microRNA targets predicts functional non-conserved and non-canonical sites. *Genome Biology*, *11*(8), 1–14. https://doi.org/10.1186/gb-2010-11-8-r90

Bhan, A., Hussain, I., Ansari, K. I., Kasiri, S., Bashyal, A., & Mandal, S. S. (2013). Antisense Transcript Long Noncoding RNA (lncRNA) HOTAIR is Transcriptionally Induced by Estradiol. *Journal of Molecular Biology*, *425*(19), 3707–3722. https://doi.org/10.1016/J.JMB.2013.01.022

Calin, G. A., Dumitru, C. D., Shimizu, M., Bichi, R., Zupo, S., Noch, E., Aldler, H., Rattan, S., Keating, M., Rai, K., Rassenti, L., Kipps, T., Negrini, M., Bullrich, F., & Croce, C. M. (2002). Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(24), 15524–15529. https://doi.org/10.1073/pnas.242606799

Carninci, P., Kasukawa, T., Katayama, S., Gough, J., Frith, M. C., Maeda, N., Oyama, R., Ravasi, T., Lenhard, B., Wells, C., Kodzius, R., Shimokawa, K., Bajic, V. B., Brenner, S. E., Batalov, S., Forrest, A. R. R., Zavolan, M., Davis, M. J., Wilming, L. G., … Hayashizaki, Y. (2005). The transcriptional landscape of the mammalian genome. *Science*, *309*(5740), 1559–1563. https://doi.org/10.1126/science.1112014

Chen, L., Heikkinen, L., Wang, C., Yang, Y., Sun, H., & Wong, G. (2019). Trends in the development of miRNA bioinformatics tools. *Briefings in Bioinformatics*, *20*(5), 1836–1852. https://doi.org/10.1093/BIB/BBY054

Chen, W., Böcker, W., Brosius, J., & Tiedge, H. (1997). Expression of neural BC200 RNA in human tumours. *The Journal of Pathology*, *183*(3). https://doi.org/10.1002/(SICI)1096-9896(199711)183:3%3C345::AID-PATH930%3E3.0.CO;2-8

Cho, W. C. S., Chow, A. S. C., & Au, J. S. K. (2011). MiR-145 inhibits cell proliferation of human lung adenocarcinoma by targeting EGFR and NUDT1. *RNA Biology* , *8*(1), 125–131. https://doi.org/10.4161/RNA.8.1.14259

Cimmino, A., Calin, G. A., Fabbri, M., Iorio, M. V., Ferracin, M., Shimizu, M., Wojcik, S. E., Aqeilan, R. I., Zupo, S., Dono, M., Rassenti, L., Alder, H., Volinia, S., Liu, C. G., Kipps, T. J., Negrini, M., & Croce, C. M. (2005). miR-15 and miR-16 induce apoptosis by targeting BCL2. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(39), 13944–13949. https://doi.org/10.1073/pnas.0506654102

Clark, M. B., Johnston, R. L., Inostroza-Ponta, M., Fox, A. H., Fortini, E., Moscato, P., Dinger, M. E., & Mattick, J. S. (2012). Genome-wide analysis of long noncoding RNA stability. *Genome Research*, *22*(5), 885–898. https://doi.org/10.1101/GR.131037.111

Davidow, L. S., Breen, M., Duke, S. E., Samollow, P. B., McCarrey, J. R., & Lee, J. T. (2007). The search for a marsupial XIC reveals a break with vertebrate synteny. *Chromosome Research*, *15*(2), 137–146. https://doi.org/10.1007/s10577-007-1121-6

Dinger, M. E., Amara, P. P., Mercer, T. R., Pang, K. C., Bruce, S. J., Gardiner, B. B., Askarian-Amiri, M. E., Ru, K., Soldà, G., Simons, C., Sunkin, S. M., Crowe, M. L., Grimmond, S. M., Perkins, A. C., & Mattick, J. S. (2008). Long noncoding RNAs in mouse embryonic stem cell pluripotency and differentiation. *Genome Research*, *18*(9), 1433–1445. https://doi.org/10.1101/GR.078378.108

Fanelli, G. N., Gasparini, P., Coati, I., Cui, R., Pakula, H., Chowdhury, B., Valeri, N., Loupakis, F., Kupcinskas, J., Cappellesso, R., & Fassan, M. (2018). LONG-NONCODING RNAs in gastroesophageal cancers. *Non-Coding RNA Research*, *3*(4), 195–212. https://doi.org/10.1016/J.NCRNA.2018.10.001

Fang, J. H., Zhou, H. C., Zeng, C., Yang, J., Liu, Y., Huang, X., Zhang, J. P., Guan, X. Y., & Zhuang, S. M. (2011). MicroRNA-29b suppresses tumor angiogenesis, invasion, and metastasis by regulating matrix metalloproteinase 2 expression. *Hepatology*, *54*(5), 1729–1740. https://doi.org/10.1002/HEP.24577

Garzon, R., & Croce, C. M. (2008). MicroRNAs in normal and malignant hematopoiesis. *Current Opinion in Hematology*, *15*(4), 352–358. https://doi.org/10.1097/MOH.0B013E328303E15D

Garzon, R., Marcucci, G., & Croce, C. M. (2010). Targeting microRNAs in cancer: rationale, strategies and challenges. *Nature Reviews Drug Discovery* , *9*(10), 775–789. https://doi.org/10.1038/nrd3179

Gatto, G., Rossi, A., Rossi, D., Kroening, S., Bonatti, S., & Mallardo, M. (2008). Epstein–Barr virus latent membrane protein 1 trans-activates miR-155 transcription through the NF-κB pathway. *Nucleic Acids Research*, *36*(20), 6608–6619. https://doi.org/10.1093/NAR/GKN666

Gejman, R., Batista, D. L., Zhong, Y., Zhou, Y., Zhang, X., Swearingen, B., Stratakis, C. A., Hedley-Whyte, E. T., & Klibanski, A. (2008). Selective Loss of MEG3 Expression and Intergenic Differentially Methylated Region Hypermethylation in the MEG3/DLK1 Locus in Human Clinically Nonfunctioning Pituitary Adenomas. *The Journal of Clinical Endocrinology & Metabolism*, *93*(10), 4119–4125. https://doi.org/10.1210/JC.2007-2633

Geng, Y. J., Xie, S. L., Li, Q., Ma, J., & Wang, G. Y. (2011). Large Intervening Non-Coding RNA HOTAIR is Associated with Hepatocellular Carcinoma Progression. *Journal of International Medical Research*, *39*(6), 2119–2128. https://doi.org/10.1177/147323001103900608

Girard, A., Sachidanandam, R., Hannon, G. J., & Carmell, M. A. (2006). A germline-specific class of small RNAs binds mammalian Piwi proteins. *Nature* , *442*(7099), 199–202. https://doi.org/10.1038/nature04917

Gong, J., Shao, D., Xu, K., Lu, Z., Lu, Z. J., Yang, Y. T., & Zhang, Q. C. (2018). RISE: a database of RNA interactome from sequencing experiments. *Nucleic Acids Research*, *46*(D1), D194–D201. https://doi.org/10.1093/NAR/GKX864

Grillone, K., Riillo, C., Riillo, C., Scionti, F., Rocca, R., Rocca, R., Tradigo, G., Guzzi, P. H., Alcaro, S., Di Martino, M. T., Tagliaferri, P., Tagliaferri, P., & Tassone, P. (2020). Non-coding RNAs in cancer: platforms and strategies for investigating the genomic “dark matter.” *Journal of Experimental & Clinical Cancer Research* , *39*(1), 1–19. https://doi.org/10.1186/S13046-020-01622-X

Gupta, R. A., Shah, N., Wang, K. C., Kim, J., Horlings, H. M., Wong, D. J., Tsai, M. C., Hung, T., Argani, P., Rinn, J. L., Wang, Y., Brzoska, P., Kong, B., Li, R., West, R. B., Van De Vijver, M. J., Sukumar, S., & Chang, H. Y. (2010). Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature* , *464*(7291), 1071–1076. https://doi.org/10.1038/nature08975

Guttman, M., Russell, P., Ingolia, N. T., Weissman, J. S., & Lander, E. S. (2013). Ribosome profiling provides evidence that large noncoding RNAs do not encode proteins. *Cell*, *154*(1), 240–251. https://doi.org/10.1016/j.cell.2013.06.009

Han, S., Liang, Y., Ma, Q., Xu, Y., Zhang, Y., Du, W., Wang, C., & Li, Y. (2019). LncFinder: an integrated platform for long non-coding RNA identification utilizing sequence intrinsic composition, structural information and physicochemical property. *Briefings in Bioinformatics*, *20*(6), 2009–2027. https://doi.org/10.1093/BIB/BBY065

Harrow, J., Denoeud, F., Frankish, A., Reymond, A., Chen, C.-K., Chrast, J., Lagarde, J., Gilbert, J. G., Storey, R., Swarbreck, D., Rossier, C., Ucla, C., Hubbard, T., Antonarakis, S. E., & Guigo, R. (2006). GENCODE: producing a reference annotation for ENCODE. *Genome Biology* , *7*(1), 1–9. https://doi.org/10.1186/GB-2006-7-S1-S4

Hensley, A. P., & McAlinden, A. (2021). The role of microRNAs in bone development. *Bone*, *143*, 115760. https://doi.org/10.1016/J.BONE.2020.115760

Hon, C. C., Ramilowski, J. A., Harshbarger, J., Bertin, N., Rackham, O. J. L., Gough, J., Denisenko, E., Schmeier, S., Poulsen, T. M., Severin, J., Lizio, M., Kawaji, H., Kasukawa, T., Itoh, M., Burroughs, A. M., Noma, S., Djebali, S., Alam, T., Medvedeva, Y. A., … Forrest, A. R. R. (2017). An atlas of human long non-coding RNAs with accurate 5′ ends. *Nature*, *543*(7644), 199–204. https://doi.org/10.1038/nature21374

Hüttenhofer, A., Brosius, J., & Bachellerie, J. P. (2002). RNomics: identification and function of small, non-messenger RNAs. *Current Opinion in Chemical Biology*, *6*(6), 835–843. https://doi.org/10.1016/S1367-5931(02)00397-6

Iorio, M. V., Ferracin, M., Liu, C. G., Veronese, A., Spizzo, R., Sabbioni, S., Magri, E., Pedriali, M., Fabbri, M., Campiglio, M., Ménard, S., Palazzo, J. P., Rosenberg, A., Musiani, P., Volinia, S., Nenci, I., Calin, G. A., Querzoli, P., Negrini, M., & Croce, C. M. (2005). MicroRNA Gene Expression Deregulation in Human Breast Cancer. *Cancer Research*, *65*(16), 7065–7070. https://doi.org/10.1158/0008-5472.CAN-05-1783

Jendrzejewski, J., He, H., Radomska, H. S., Li, W., Tomsic, J., Liyanarachchi, S., Davuluri, R. V., Nagy, R., & De La Chapelle, A. (2012). The polymorphism rs944289 predisposes to papillary thyroid carcinoma through a large intergenic noncoding RNA gene of tumor suppressor type. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(22), 8646–8651. https://doi.org/10.1073/pnas.120565410

Ji, P., Diederichs, S., Wang, W., Böing, S., Metzger, R., Schneider, P. M., Tidow, N., Brandt, B., Buerger, H., Bulk, E., Thomas, M., Berdel, W. E., Serve, H., & Müller-Tidow, C. (2003). MALAT-1, a novel noncoding RNA, and thymosin β4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene* , *22*(39), 8031–8041. https://doi.org/10.1038/sj.onc.1206928

John, B., Enright, A. J., Aravin, A., Tuschl, T., Sander, C., & Marks, D. S. (2004). Human MicroRNA Targets. *PLOS Biology*, *2*(11), e363. https://doi.org/10.1371/JOURNAL.PBIO.0020363

Jones-Rhoades, M. W., & Bartel, D. P. (2004). Computational Identification of Plant MicroRNAs and Their Targets, Including a Stress-Induced miRNA. *Molecular Cell*, *6*(14), 787–799. https://doi.org/10.1016/J.MOLCEL.2004.05.027

Junker, A., Krumbholz, M., Eisele, S., Mohan, H., Augstein, F., Bittner, R., Lassmann, H., Wekerle, H., Hohlfeld, R., & Meinl, E. (2009). MicroRNA profiling of multiple sclerosis lesions identifies modulators of the regulatory protein CD47. *Brain*, *132*(12), 3342–3352. https://doi.org/10.1093/BRAIN/AWP300

Kiriakidou, M., Nelson, P. T., Kouranov, A., Fitziev, P., Bouyioukos, C., Mourelatos, Z., & Hatzigeorgiou, A. (2004). A combined computational-experimental approach predicts human microRNA targets. *Genes & Development*, *18*(10), 1165–1178. https://doi.org/10.1101/GAD.1184704

Klenov, M. S., Lavrov, S. A., Stolyarenko, A. D., Ryazansky, S. S., Aravin, A. A., Tuschl, T., & Gvozdev, V. A. (2007). Repeat-associated siRNAs cause chromatin silencing of retrotransposons in the Drosophila melanogaster germline. *Nucleic Acids Research*, *35*(16), 5430–5438. https://doi.org/10.1093/NAR/GKM576

Kong, L., Zhang, Y., Ye, Z. Q., Liu, X. Q., Zhao, S. Q., Wei, L., & Gao, G. (2007). CPC: assess the protein-coding potential of transcripts using sequence features and support vector machine. *Nucleic Acids Research*, *35*(suppl_2), W345–W349. https://doi.org/10.1093/NAR/GKM391

Kong, W., He, L., Coppola, M., Guo, J., Esposito, N. N., Coppola, D., & Cheng, J. Q. (2010). MicroRNA-155 Regulates Cell Survival, Growth, and Chemosensitivity by Targeting FOXO3a in Breast Cancer. *Journal of Biological Chemistry*, *285*(23), 17869–17879. https://doi.org/10.1074/JBC.M110.101055

Krek, A., Grün, D., Poy, M. N., Wolf, R., Rosenberg, L., Epstein, E. J., MacMenamin, P., Da Piedade, I., Gunsalus, K. C., Stoffel, M., & Rajewsky, N. (2005). Combinatorial microRNA target predictions. *Nature Genetics*, *37*(5), 495–500. https://doi.org/10.1038/ng1536

Krüger, J., & Rehmsmeier, M. (2006). RNAhybrid: microRNA target prediction easy, fast and flexible. *Nucleic Acids Research*, *34*(suppl_2), W451–W454. https://doi.org/10.1093/NAR/GKL243

Lai, E. C. (2003). microRNAs: Runts of the Genome Assert Themselves. *Current Biology*, *13*(23), R925–R936. https://doi.org/10.1016/J.CUB.2003.11.017

Leão, R., Albersen, M., Looijenga, L. H. J., Tandstad, T., Kollmannsberger, C., Murray, M. J., Culine, S., Coleman, N., Belge, G., Hamilton, R. J., & Dieckmann, K. P. (2021). Circulating MicroRNAs, the Next-Generation Serum Biomarkers in Testicular Germ Cell Tumours: A Systematic Review. *European Urology*, *80*(4), 456–466. https://doi.org/10.1016/J.EURURO.2021.06.006

Lee, J., & Kang, H. (2022). Role of MicroRNAs and Long Non-Coding RNAs in Sarcopenia. *Cells*, *11*(2), 187. https://doi.org/10.3390/CELLS11020187

Lewis, B. P., Burge, C. B., & Bartel, D. P. (2005). Conserved Seed Pairing, Often Flanked by Adenosines, Indicates that Thousands of Human Genes are MicroRNA Targets. *Cell*, *1*(120), 15–20. https://doi.org/10.1016/J.CELL.2004.12.035

Li, A., Zhang, J., & Zhou, Z. (2014). PLEK: a tool for predicting long non-coding RNAs and messenger RNAs based on an improved k-mer scheme. *BMC Bioinformatics*, *15*: 311. https://doi.org/10.1186/1471-2105-15-311

Lin, Q., Shi, Y., Liu, Z., Mehrpour, M., Hamaï, A., & Gong, C. (2022). Non-coding RNAs as new autophagy regulators in cancer progression. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, *1868*(1), 166293. https://doi.org/10.1016/J.BBADIS.2021.166293

Lorenz, R., Bernhart, S. H., Höner zu Siederdissen, C., Tafer, H., Flamm, C., Stadler, P. F., & Hofacker, I. L. (2011). ViennaRNA Package 2.0. *Algorithms for Molecular Biology*, *6*(1), 1–14. https://doi.org/10.1186/1748-7188-6-26

Losko, M., Kotlinowski, J., & Jura, J. (2016). Long noncoding RNAs in metabolic syndrome related disorders. *Mediators of Inflammation*, *2016*. https://doi.org/10.1155/2016/5365209

Lund, E., Güttinger, S., Calado, A., Dahlberg, J. E., & Kutay, U. (2004). Nuclear Export of MicroRNA Precursors. *Science*, *303*(5654), 95–98. https://doi.org/DOI: 10.1126/science.1090599

Lv, X. Bin, Lian, G. Y., Wang, H. R., Song, E., Yao, H., & Wang, M. H. (2013). Long Noncoding RNA HOTAIR Is a Prognostic Marker for Esophageal Squamous Cell Carcinoma Progression and Survival. *PLOS ONE*, *8*(5), e63516. https://doi.org/10.1371/JOURNAL.PONE.0063516

Ma, L., Cao, J., Liu, L., Du, Q., Li, Z., Zou, D., Bajic, V. B., & Zhang, Z. (2019). LncBook: a curated knowledgebase of human long non-coding RNAs. *Nucleic Acids Research*, *47*(5), 2699–2699. https://doi.org/10.1093/NAR/GKZ073

MacRae, I. J., Zhou, K., Li, F., Repic, A., Brooks, A. N., Cande, W. Z., Adams, P. D., & Doudna, J. A. (2006). Structural basis for double-stranded RNA processing by Dicer. *Science*, *311*(5758), 195–198. https://doi.org/10.1126/science.1121638

Mariner, P. D., Walters, R. D., Espinoza, C. A., Drullinger, L. F., Wagner, S. D., Kugel, J. F., & Goodrich, J. A. (2008). Human Alu RNA Is a Modular Transacting Repressor of mRNA Transcription during Heat Shock. *Molecular Cell*, *29*(4), 499–509. https://doi.org/10.1016/J.MOLCEL.2007.12.013

Martins, M., Rosa, A., Guedes, L. C., Fonseca, B. V., Gotovac, K., Violante, S., Mestre, T., Coelho, M., RosaMá, M. M., Martin, E. R., Vance, J. M., Outeiro, T. F., Wang, L., Borovecki, F., Ferreira, J. J., & Oliveira, S. A. (2011). Convergence of miRNA Expression Profiling, α-Synuclein Interacton and GWAS in Parkinson's Disease. *PLOS ONE*, *6*(10), e25443. https://doi.org/10.1371/JOURNAL.PONE.0025443

Matouk, I. J., DeGroot, N., Mezan, S., Ayesh, S., Abu-Lail, R., Hochberg, A., & Galun, E. (2007). The H19 Non-Coding RNA Is Essential for Human Tumor Growth. *PLOS ONE*, *2*(9), e845. https://doi.org/10.1371/JOURNAL.PONE.0000845

Mercer, T. R., Dinger, M. E., & Mattick, J. S. (2009). Long non-coding RNAs: insights into functions. *Nature Reviews Genetics* , *10*(3), 155–159. https://doi.org/10.1038/nrg2521

Morishita, A., Oura, K., Tadokoro, T., Fujita, K., Tani, J., & Masaki, T. (2021). MicroRNAs in the Pathogenesis of Hepatocellular Carcinoma: A Review. *Cancers* , *13*(3), 514. https://doi.org/10.3390/CANCERS13030514

Mourtada-Maarabouni, M., Pickard, M. R., Hedge, V. L., Farzaneh, F., & Williams, G. T. (2008). GAS5, a non-protein-coding RNA, controls apoptosis and is downregulated in breast cancer. *Oncogene* , *28*(2), 195–208. https://doi.org/10.1038/onc.2008.373

Ng, S. Y., & Stanton, L. W. (2013). Long non-coding RNAs in stem cell pluripotency. *Wiley Interdisciplinary Reviews: RNA*, *4*(1), 121–128. https://doi.org/10.1002/WRNA.1146

Ozcan, G., Ozpolat, B., Coleman, R. L., Sood, A. K., & Lopez-Berestein, G. (2015). Preclinical and clinical development of siRNA-based therapeutics. *Advanced Drug Delivery Reviews*, *87*, 108–119. https://doi.org/10.1016/J.ADDR.2015.01.007

Papadopoulos, G. L., Reczko, M., Simossis, V. A., Sethupathy, P., & Hatzigeorgiou, A. G. (2009). The database of experimentally supported targets: a functional update of TarBase. *Nucleic Acids Research*, *37*(suppl_1), D155–D158. https://doi.org/10.1093/NAR/GKN809

Pierce, J. B., Zhou, H., Simion, V., & Feinberg, M. W. (2022). Long Noncoding RNAs as Therapeutic Targets. In S. Carpenter (Ed.), *Advances in Experimental Medicine and Biology* (Vol. 1363, pp. 161–175). Springer. https://doi.org/10.1007/978-3-030-92034-0_9

Romero-Barrios, N., Legascue, M. F., Benhamed, M., Ariel, F., & Crespi, M. (2018). Splicing regulation by long noncoding RNAs. *Nucleic Acids Research*, *46*(5), 2169–2184. https://doi.org/10.1093/NAR/GKY095

Rusinov, V., Baev, V., Minkov, I. N., & Tabler, M. (2005). MicroInspector: a web tool for detection of miRNA binding sites in an RNA sequence. *Nucleic Acids Research*, *33*(suppl_2), W696–W700. https://doi.org/10.1093/NAR/GKI364

Saito, K., Ishizuka, A., Siomi, H., & Siomi, M. C. (2005). Processing of Pre-microRNAs by the Dicer-1–Loquacious Complex in Drosophila Cells. *PLOS Biology*, *3*(7), e235. https://doi.org/10.1371/JOURNAL.PBIO.0030235

Sethupathy, P., Corda, B., & Hatzigeorgiou, A. G. (2006). TarBase: A comprehensive database of experimentally supported animal microRNA targets. *RNA*, *12*(2), 192–197. https://doi.org/10.1261/RNA.2239606

Small, E. M., & Olson, E. N. (2011). Pervasive roles of microRNAs in cardiovascular biology. *Nature* , *469*(7330), 336–342. https://doi.org/10.1038/nature09783

Staněk, D., & Neugebauer, K. M. (2006). The Cajal body: a meeting place for spliceosomal snRNPs in the nuclear maze. *Chromosoma* , *115*(5), 343–354. https://doi.org/10.1007/S00412-006-0056-6

Statello, L., Guo, C. J., Chen, L. L., & Huarte, M. (2020). Gene regulation by long non-coding RNAs and its biological functions. *Nature Reviews Molecular Cell Biology* , *22*(2), 96–118. https://doi.org/10.1038/s41580-020-00315-9

Sun, L., Liu, H., Zhang, L., & Meng, J. (2015). lncRScan-SVM: A Tool for Predicting Long Non-Coding RNAs Using Support Vector Machine. *PLOS ONE*, *10*(10), e0139654. https://doi.org/10.1371/JOURNAL.PONE.0139654

Sun, M., Jin, F. yan, Xia, R., Kong, R., Li, J. hai, Xu, T. peng, Liu, Y. wen, Zhang, E. bao, Liu, X. hua, & De, W. (2014). Decreased expression of long noncoding RNA GAS5 indicates a poor prognosis and promotes cell proliferation in gastric cancer. *BMC Cancer*, *14*(1), 1–12. https://doi.org/10.1186/1471-2407-14-319

The RNAcentral Consortium. (2019). RNAcentral: a hub of information for non-coding RNA sequences. *Nucleic Acids Research*, *47*(D1), D221–D229. https://doi.org/10.1093/NAR/GKY1034

Toden, S., & Goel, A. (2022). Non-coding RNAs as liquid biopsy biomarkers in cancer. *British Journal of Cancer*, *126*(3), 351–360. https://doi.org/10.1038/s41416-021-01672-8

Wang, L., Zeng, X., Chen, S., Ding, L., Zhong, J., Zhao, J. C., Wang, L., Sarver, A., Koller, A., Zhi, J., Ma, Y., Yu, J., Chen, J., & Huang, H. (2013). BRCA1 is a negative modulator of the PRC2 complex. *The EMBO Journal*, *32*(11), 1584–1597. https://doi.org/10.1038/EMBOJ.2013.95

Wienholds, E., & Plasterk, R. H. A. (2005). MicroRNA function in animal development. *FEBS Letters*, *579*(26), 5911–5922. https://doi.org/10.1016/J.FEBSLET.2005.07.070

Wolff, T., Menssen, R., Hammel, J., & Bindereif, A. (1994). Splicing function of mammalian U6 small nuclear RNA: conserved positions in central domain and helix I are essential during the first and second step of pre-mRNA splicing. *Proceedings of the National Academy of Sciences*, *91*(3), 903–907. https://doi.org/10.1073/PNAS.91.3.903

Xia, T., O'Hara, A., Araujo, I., Barreto, J., Carvalho, E., Sapucaia, J. B., Ramos, J. C., Luz, E., Pedroso, C., Manrique, M., Toomey, N. L., Brites, C., Dittmer, D. P., & Harrington, W. J. (2008). EBV MicroRNAs in Primary Lymphomas and Targeting of CXCL-11 by ebv-mir-BHRF1-3. *Cancer Research*, *68*(5), 1436–1442. https://doi.org/10.1158/0008-5472.CAN-07-5126

Yi, R., Qin, Y., Macara, I. G., & Cullen, B. R. (2003). Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs. *Genes & Development*, *17*(24), 3011–3016. https://doi.org/10.1101/GAD.1158803

Yoshikawa, M., Peragine, A., Mee, Y. P., & Poethig, R. S. (2005). A pathway for the biogenesis of trans-acting siRNAs in Arabidopsis. *Genes & Development*, *19*(18), 2164–2175. https://doi.org/10.1101/GAD.1352605

Zhao, J., Song, X., & Wang, K. (2016). lncScore: alignment-free identification of long noncoding RNA from assembled novel transcripts. *Scientific Reports 2016 6:1*, *6*(1), 1–12. https://doi.org/10.1038/srep34838

Zhao, J., Sun, B. K., Erwin, J. A., Song, J. J., & Lee, J. T. (2008). Polycomb proteins targeted by a short repeat RNA to the mouse X chromosome. *Science*, *322*(5902), 750–756. https://doi.org/10.1126/science.1163045

Zhao, Y., & Srivastava, D. (2007). A developmental view of microRNA function. *Trends in Biochemical Sciences*, *32*(4), 189–197. https://doi.org/10.1016/j.tibs.2007.02.006

Zheng, H. T., Shi, D. B., Wang, Y. W., Li, X. X., Xu, Y., Tripathi, P., Gu, W. L., Cai, G. X., & Cai, S. J. (2014). High expression of lncRNA MALAT1 suggests a biomarker of poor prognosis in colorectal cancer. *International Journal of Clinical and Experimental Pathology*, *7*(6), 3174. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4097248/