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Long non-coding RNAs and cancer: a new frontier of translational research?

R Spizzo[1], **MI Almeida**[2,3], **A Colombatti**[1], and **GA Calin**[2]

[1]Experimental Oncology, Centro di Riferimento Oncologico, IRCSS-National Cancer Institute, Aviano (PN), Italy

[2]Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[3]Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal

Abstract

Tiling array and novel sequencing technologies have made available the transcription profile of the entire human genome. However, the extent of transcription and the function of genetic elements that occur outside of protein-coding genes, particularly those involved in disease, are still a matter of debate. In this review, we focus on long non-coding RNAs (lncRNAs) that are involved in cancer. We define lncRNAs and present a cancer-oriented list of lncRNAs, list some tools (for example, public databases) that classify lncRNAs or that scan genome spans of interest to find whether known lncRNAs reside there, and describe some of the functions of lncRNAs and the possible genetic mechanisms that underlie lncRNA expression changes in cancer, as well as current and potential future applications of lncRNA research in the treatment of cancer.

Keywords

long non-coding RNAs; cancer; online databases; function

INTRODUCTION

Non-protein-coding RNAs (ncRNAs) are gaining the attention of researchers in many fields, and the number of published articles is exponentially growing.[1] MicroRNAs (miRNAs) belong to a small ncRNA group and are the most studied among ncRNAs; however, many more types of ncRNAs exist. In fact, tiling array and novel sequencing technologies have made available the transcription profile of the entire human genome, which showed a widespread transcription activity.[2] However, the extent of transcription (that is, whether ncRNAs are mainly localized in close proximity to protein-coding genes (PCGs) or widespread throughout the genome) and the function of genetic elements that occur outside of PCGs are still a matter of debate.[3–5] Moreover, by more traditional means, several researchers have cloned RNA transcripts whose nature is probably not to code proteins and

Correspondence: Dr GA Calin, Department of Experimental Therapeutics, Unit 1950, The University of Texas MD Anderson Cancer Center, 1901 East Road, Houston, TX 77030, USA., gcalin@mdanderson.org.

CONFLICT OF INTEREST
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that have a longer sequence than miRNAs do. These can be grouped under the classification of long ncRNAs (lncRNAs).

The human genome census reveals a striking predominance of non-coding regions (http://www.ncrna.org/statgenome/index.html?view=class&gid=hg18). In fact, PCG exons represent about 1.6% of the 3×10^9 base pairs of the human genome. Moreover, the number of PCGs is quite steady during evolution in metazoa (G value paradox), whereas the size of genomes tends to increase.[6] Conservation among genomes also occurs within intergenic regions, suggesting that these regions are important in the fundamental processes involved in life. Finally, the largest part of the human genome, about 46%, is made up of repetitive elements (such as transposons) that probably have been one of the driving forces of evolution.[7] It is worth mentioning that in most cases transposons do not code for proteins, and recently they have been found to be related to cancer processes.[8,9]

In this review, we focus our attention on lncRNAs that are involved in cancer. First, we will define lncRNA and present a cancer-oriented list of lncRNAs. Second, we will list some tools (for example, public databases) that classify lncRNAs or that scan genome spans of interest to find whether known lncRNAs reside there. Some of the databases can also be used to search for lncRNAs that are involved in a process or disease of interest (for example, cancer). Finally, we will describe some of the functions of lncRNAs, possible genetic mechanisms that underlie lncRNA expression changes in cancer, and current and potential future applications of lncRNA research in the treatment of cancer.

DEFINITION OF lncRNA

The most commonly used definition of lncRNA is an RNA molecule that is longer than 200 nucleotides and that is not translated into a protein. However, this definition may be too simple and does not take into account certain issues. First, the cutoff of 200 nucleotides was arbitrarily chosen and it was set more on the basis of RNA binding to silica columns during RNA purification rather than for its functional meaning.[2] Second, a PCG is usually defined as a transcript that contains an open reading frame (ORF) longer than 100 amino acids.[10] However, lncRNAs can contain ORFs longer than 100 amino acids and not necessarily synthesize polypeptides; plus, polypeptides shorter than 100 amino acids can be functional in organisms and are not by-products of canonical proteins.[11] Finally, and even more confounding, the same RNA can contain both PCGs and non-coding functions.[12–14] These issues demonstrate how little we currently know about ncRNAs (particularly lncRNAs) and how difficult it is to form a definition.

One updated definition that we agree with takes into account some of the aforementioned issues[15] and defines lncRNAs as RNA molecules that may function as either primary or spliced transcripts and do not fit into known classes of small RNAs, such as miRNAs, piwi-interacting RNAs and small nucleolar RNAs, or into classes of structural RNAs (for example, transfer RNAs, small nuclear RNAs and spliceosomal RNAs). The strengths of this definition are the absence of ORF restriction, given the fact that a RNA molecule can possess both coding and non-coding activities, and the absence of length restriction that was arbitrarily set. Other investigators have proposed bioinformatic tools to clarify or adjust the 100-amino acid ORF length cutoff to determine whether an RNA molecule codes for a protein (reviewed in Dinger *et al.*).[10] The strengths of Mercer's definition are the absence of ORF restriction, as a matter of fact a RNA molecule can possess both coding and non-coding activities, and the absence of length restriction that was arbitrarily set.

Additionally, we must point out that in this review we use the abbreviation lncRNA, which should not be confused with long intergenic ncRNAs (lincRNAs)[16,17], which are a subtype of lncRNAs.

CLASSIFICATION OF LNCRNAS AND PUBLIC DATABASES

Generating comprehensive classifications of lncRNAs is not an easy task. In fact, many lncRNA classifications are annotations from larger databases or projects (for example, GeneBank, Fantom3), and information about the real nature (protein-coding, non-protein-coding or mixed) and function of lncRNAs cannot be gleaned from these sources. Similarly, some lncRNAs have been described in only one published study and no further reports exist.[18,19] Some lncRNAs have been grouped on the basis of their position relative to host PCG (for example, overlapping RNA, cis-antisense RNA, antisense RNA, bidirectional RNA, intronic RNA, promoter- or enhancer-correlated RNA).[15] As it usually happens for all classifications, the same lncRNA may be listed under different groups. For example, lncRNAs predicted by computational models (for example, RNAz or Evofold) are often listed under different names in databases obtained from sequencing projects.

To facilitate the difficult task of organizing lncRNAs, we have listed the current online databases that include ncRNAs (Table 1). These databases collect lncRNAs originated from GenBank annotations or from published articles. Some of these databases list both ncRNAs that have been experimentally proven and those that are purely computational predictions (based on RNA Z or Evofold) or have been annotated as ncRNAs on the basis of the predicted size of their ORFs.

We found the functional RNA project database (fRNA) worth visiting. It uses a University of California Santa Cruz genome browser interface that contains many ncRNA tracks that have already been set up in a Genome Browser graphic interface, which allows the user to search for specific ncRNAs along with other features in the genomic context of interest. Although both fRNA and the Noncode project allow the user to search for functional classes or processes (for example, find all known ncRNAs that are involved in the cell cycle or in DNA replication or transcription), fRNA allows the user to search by disease (for example, cancer) as well. The ncRNA expression database, on the other hand, contains a large data set of ncRNA expression profiles that were obtained from three different experiment sets: Allen Brain Atlas (mouse), GNF Atlas (mouse and human) and V1.0 Compugen array (mouse). Although these expression data sets are not cancer-oriented, we foresee that eventually the ncRNA expression database, as well as others that are listed in Table 1, will be matched with other data sets that are more cancer-oriented (for example, Oncomine; https://www.oncomine.org). For now, the genomic positions of several lncRNAs can be matched to databases that collect lists of single-nucleotide polymorphisms (SNPs) associated with cancer (http://cistrome.dfci.harvard.edu/CaSNP/; Hindorff *et al.*)[172] or cancer-associated genetic regions (for example, http://cancergenome.nih.gov, http://decipher.sanger.ac.uk, the Cancer Workbench at https://cgwb.nci.nih.gov/cgi-bin/heatmap and National Center for Biotechnology Information Gene Expression Omnibus at http://www.ncbi.nlm.nih.gov/geo/).[14,27]

CANCER-RELATED LNCRNAS

In this review, we focused our efforts on developing a list of lncRNAs that have been linked to cancer by various means. We mainly used three of the online databases to retrieve lncRNAs (that is, the LncRNA database, Noncode and the RNA Database), and we searched Pubmed for articles linking these lncRNAs to cancer. In Table 2, we report our findings.

In some cases the link between the lncRNA and cancer was obvious, and cancer was actually the model where these lncRNAs were first described for the first time (for example, MALAT-1, PCA3/DDR3 and HOTAIR). However, we also found some lncRNAs for which a link to cancer has not yet been fully elucidated, but preliminary findings indicate that it could be worthwhile to investigate the possible connection (these lncRNAs are marked with

an asterisk in Table 2). For example, the lncRNA Air (antisense to Igf2r RNA) is involved in the imprinting of the Igfr2 locus.[31] Despite the association of Igfr2 with cancer[138] and the association of Air with Igfr2,[139] we did not find any articles that directly examine the relationship between Air and cancer in humans. Moreover, although alpha 250/alpha 280 lncRNA regulates RPS14 transcription, which has been shown in short hairpin RNA screens to be a causal factor in 5q- syndrome,[33] no studies have yet examined the direct involvement of alpha 250/alpha 280 lncRNA in 5q-syndrome.[140]

Some lncRNAs that we included contain small ncRNA (for example, miRNA and small nucleolar RNA). Although these lncRNAs host small RNAs, this may not be their exclusive function. For example, the knockout model of LEU2, which includes miR-15/16 as well, showed a more aggressive phenotype than did the miR-15/16 knockout model, which may indicate that LEU2 can participate in chronic lymphocytic leukemia development.[80]

Some lncRNAs have been associated with cancer but are not listed in the public data sets that we used to prepare Table 2. For example, regions that are extremely conserved among human, mouse and rat genomes[141] are expressed in cancer tissue differently than in normal tissues and are regulated by methylation as well.[142–146] The extremely high level of conservation among these lncRNAs, which are referred to as ultraconserved genes or transcribed UCRs, is their most peculiar feature.

LNCRNA FUNCTION

The function of ncRNAs is the most difficult and least understood aspect of ncRNA research. Better understanding ncRNA function will help clarify the real impact of genomic pervasive transcription on cell biology and evolution.[147] As we gathered information about the lncRNAs involved in cancer, we also collected examples of lncRNA function (Figure 1).

The first example that we describe is for lincRNAs. LincRNAs were first described using histone mark signatures, specifically trimethylation in lysine 4 and lysine 36 of histone 3 (H3K4m3, H3K36m3 or simply K4K36). The K4K36 mark detects active transcription units of both PCGs and ncRNAs. After excluding known genes (PCGs and ncRNAs), researchers have been able to retrieve novel transcriptional units. The first reports analyzed mouse and human cell lines, uncovering about 3000 lincRNAs.[16,148] However, many more lincRNAs may remain to be discovered in other settings.[149] Certain, lincRNAs were discovered before the use of the K4K36 signature such as MALAT-1[82] and HOTAIR, which was the first lncRNA ever described to interact with polycomb proteins and suppress gene transcription.[64] Moreover, other histone signatures might reveal new lncRNAs.[150]

About 20% of lincRNAs bind to polycomb repressive complex 2, indicating that lincRNAs might regulate gene expression by directing the polycomb protein group to target DNA regions, inducing changes in histone marks and chromatin structure and ultimately suppressing transcription activity.[148,151] The current model proposes that lincRNAs directly bind to the polycomb proteins and direct them to specific DNA segments in the human genome. However, how the lincRNA-polycomb complex recognizes the target DNA is not currently known.[152] We do not currently know whether transcription factors bind lincRNAs as well, and whether RNA-binding proteins regulate lincRNAs as they do with miRNAs.[153]

Another class of lncRNAs that seems to regulate gene expression by changes in chromatin status includes antisense transcripts (reviewed in Morris and Vogt).[154] Antisense ncRNA transcripts overlap PCG but are transcribed in the opposite direction. Although one would expect small interfering RNA (siRNA) machinery to degrade messenger RNA after the sense–antisense pairing, the mechanism in act instead seems to be the modifications of histone marks at the promoter region of the sense transcript (that is, PCGs). Apparently,

antisense lncRNAs drive (cytosine-5)-methyltransferase 3A (DNMT3A) to the DNA of the host PCG to methylate histones at lysine 9 and 27 or CpG islands and ultimately silence transcription.

Several oncogenes or tumor-suppressor genes exhibit antisense transcription and consequent transcription gene silencing (for example, *p21*, *c-Myc*, *p15*, *p53*, *TIE1* and *PU.1*).[35] Interestingly, exogenous siRNAs that are in antisense orientation compared with PCG promoters are also effective at silencing transcription.[155] However, how the antisense lncRNAs are regulated has not yet been explored.

LincRNAs, antisense lncRNAs, and other lncRNAs[44,156] can be classified among the chromatin-associated RNAs (CARs) because their function apparently relies on the ability of the RNA to somehow bind to genomic DNA and consequently regulate chromatin states (euchromatin versus heterochromatin).[44,156] Mondal *et al.*[43] performed a thorough investigation of CARs throughout the genome of a human skin fibroblast cell line by deep sequencing of DNA-associated RNA after micrococcal nuclease treatment. They identified several CARs and reported that one CAR can activate transcription of neighboring genes.

Another class of lncRNAs that seems to regulate the transcription activity of host PCGs comprises the promoter upstream transcripts (PROMPTs). PROMPTs are localized upstream of promoters of some PCGs and they can be transcribed in both the sense and antisense orientations. PROMPTs seem to be a byproduct of RNA pol II activity; however, preliminary findings suggest that PROMPTs control promoter methylation.[45] When Preker *et al.* first described PROMPT existence, they used a peculiar approach: they inhibited exosome key proteins by using siRNA to prolong the half-life of short-lived RNA transcripts. In this way, they were able to identify a plethora of PROMPTs. However, the function and impact of PROMPTs in cell biology have not yet been explored.

It is possible that lincRNAs, PROMPTs, and antisense RNAs, or CARs in general, have interdependent functions. For example, antigene RNAs are synthetic RNA molecules that when designed to be complementary to PCG promoters can either repress or activate gene expression. Antigene RNAs rely on RNA–RNA interaction with antisense transcripts that are generated nearby targeted promoters and on Ago proteins binding.[157] It is possible that PROMPTs, lincRNAs and antisense lncRNAs interact and recapitulate antigene RNA mechanism; it is known that PROMPTs and antisense lncRNAs can interact with each other to trigger the antigene RNA pathway.[158] In another example of lncRNA interdependent function, lincRNAs can interact with PROMPTs or antisense lncRNAs to ultimately direct polycomb protein complexes to targeted promoters of PCGs.[36] Further examples of lncRNA function are discussed in other reviews.[159,160]

LNCRNA NETWORKS

Another interesting lncRNA function is target decoy or mimicry: lncRNAs can deceive another RNA or protein away from its natural target. For example, Poliseno *et al.*[14] described pseudogenes as decoys for miRNAs. They reported that the *PTEN* gene and the PTEN pseudogenes (PTENP1) share a high degree of sequence homology and are targeted by the same miRNAs (that is, miR-17, -21, -214, -9 and -26 families). Thus, changes in PTENP1 expression levels indirectly affect PTEN expression levels by sequestering *PTEN*-targeting miRNAs. For instance, if PTENP1 expression levels decrease, miRNAs will be able to target *PTEN* and ultimately downregulate PTEN expression levels. Poliseno *et al.*[14] also noted a similar mechanism for RAS pseudogenes. Another example of a lncRNA that acts as a miRNA decoy is the highly upregulated liver cancer transcript (HULC), which binds to and inhibits miR-372.[76]

Target decoys occur not only in cancer but also in infectious diseases: two studies reported that virus-encoded transcripts can act as miRNA decoys; in this case the net effect was to sequester and downregulate the miRNAs of the host organism.[161,162] A similar example exists in plants for endogenous pseudogene transcripts that share a high degree of sequence homology with PCG transcripts, although in this case the pseudogenes contain point mutations within the miRNA-binding sites. Apparently, these pseudogenes not only sequester miRNAs from their PCG target, but also reduce miRNA expression levels.[163]

One particular type of lncRNA decoy involves proteins. PROMPTs, such as GAS5, can bind to transcription-factor proteins that would otherwise bind to the DNA promoters; thus, the RNA transcript decoy sequesters the transcription factor, which is no longer able to affect downstream target genes.[164] GAS5 accomplishes this with a stem-loop structure in its sequence resembling the glucocorticoid receptor DNA-binding element. GAS5 seems to regulate other receptors (that is, androgen, mineralcorticoid and progesterone) by the same means. Interestingly, the interaction between GAS5 and the glucocorticoid receptor is modulated by dexamethasone, a glucocorticoid receptor agonist.[164] At the same time, GAS5 has been shown to be regulated by mammalian target of rapamycin pathway and to mediate rapamycin effect on cell cycle in T cells (reviewed in Williams *et al*.).[165]

NcRNA decoys can target not only ncRNA–mRNA or DNA–protein interactions, but also interactions between ncRNAs. For example, miRNAs can target other ncRNAs as they do with messenger RNA; Calin *et al*.[144] showed that miR-155 targets transcribed UCRs in both *in vitro* models and chronic lymphocytic leukemia patients. These findings support the existence of networks among ncRNAs and between ncRNAs and PCGs that are involved in cancer.

LNCRNA EXPRESSION IN CANCER

In cancer biology, one of the first evidences that researchers seek is gene expression differences between tumor and normal samples. The breadth of knowledge concerning lncRNA expression profiles in tumor and normal samples is quite modest at this time. It is likely that commercial gene expression arrays that have been used for PCGs contain probes that hybridize to lncRNAs, and it may be possible to retrieve cancer-related lncRNA expression profiles from public, tumor-specific gene-expression data sets (for example, Oncomine, Gene Expression Omnibus). However, to our knowledge this has not yet been done.

To identify novel transcripts, some investigators have used the Affymetrix tiling array, which can test for lncRNA gene expression.[166,167] Others have performed custom array profiling on large sample sets of a few lncRNAs.[144,168] Most articles concerning lncRNA expression in cancer have shown a selected number of lncRNAs probed in tumor samples (Table 2 lists tumor types that have been tested for lncRNA expression). We also found a few articles (not included in Table 2) reporting the existence of transcriptionally active regions that are located outside known PCGs and are differentially expressed between normal and tumor tissues or are expressed under stress conditions.[166,167] Gibb *et al*. used SAGE library generation to compare lncRNA expression in normal and dysplastic oral mucosa.[169]

Cancer biologists also seek to uncover genetic mutations (for example, amplifications, deletions and sequence mutations) in the lncRNA sequence. For example, sequence mutations in RNA component of mitochondrial RNA processing endoribonu-clease (RMRP) lncRNA are responsible for cartilage-hair hypoplasia syndrome, which is also known to increase the risk of developing several types of tumors.[170,171] Some investigators have already sequenced select classes of lncRNAs to find mutations.[166,172]

In recent years, using SNP arrays to study very large populations (in the thousands), researchers have discovered several SNPs that are associated with certain traits or diseases, such as cancer (http://www.genome.gov/gwastudies contains a list of SNPs associated with several diseases).[173] In some cases, disease-associated SNPs are in genomic spans outside of PCG transcripts;[174,175] these genomic spans would be good candidates regions to search for novel transcripts. Some researchers have already found SNPs that are located within lncRNA transcripts and are associated with cancer. For example, Yang *et al*. showed that among six SNPs that are located within the boundaries of UCRs, two of them (that is, rs2056116 and rs9572903) were significantly associated with familial breast cancer.[176] Cabili *et al*.,[27] while reporting on a census of 8195 lincRNAs in 24 different human tissues, noted that the genomic positions of 414 lncRNAs were related to SNPs that have been associated with several diseases.[173]

DIAGNOSTIC AND THERAPEUTIC APPLICATIONS OF LNCRNAS

The relatively new field of lncRNA research is expanding quickly, but many gaps still need to be filled. Only recently has the number of lncRNAs in the human genome become clear.[27] Moreover, researchers have not extensively investigated lncRNA expression in large and clinically controlled tumor data sets, nor is lncRNA function well understood.[149] Few examples of transgenic models of lncRNA have been published to date.[80,177]

We foresee potential uses of lncRNAs in the clinical setting for oncology or for other fields. LncRNAs may be useful as novel biomarkers for diagnosis, prognosis and prediction of response to therapy. The lncRNA PCA3/DD3, for example, has already been assayed in controlled clinical settings. PCA3/DD3 was originally discovered in a differential display analysis comparing normal and tumor prostate samples.[178] The features that make PCA3/DD3 a promising biomarker are its unique expression profile in prostate tumors compared with normal prostate and other tissues, its highly increased expression levels (that is, about 60 times) in prostate tumors compared with normal tissues, its expression in early-stage tumors and detectability in urine. PCA3/DD3 has been tested as a biomarker in clinical trials and compared with standard prostate markers (that is, prostate-specific antigen). However, the effectiveness of PC3/DD3 as a biomarker was about the same as that of prostate-specific antigen.[106,179]

The marked increase or decrease in lncRNA expression levels in tumors compared with normal tissues seems to be a feature shared among lncRNAs. Indeed, HOTAIR was found to be upregulated by hundreds or thousands of times in metastatic breast cancer tissue compared with normal breast tissue.[64] Such a large difference in lncRNA expression levels in tumors compared with normal tissues is a topic for future clinical research, although lncRNAs must be assayed in larger clinical data sets. Other lncRNAs might be promising biomarkers as well.[106,179]

Another potential avenue of lncRNA research relates to the discovery of circulating miRNAs in serum, plasma and other body fluids, demonstrating that miRNAs may act not only within cells, but also at other sites within the body.[180] It is highly probable that other types of ncRNAs, including lncRNAs, can be present in body fluids, as suggested by, for example, their presence in the secreted exosomes. LncRNAs found in numerous quantities in body fluids could be detected using simple quantitative reverse transcriptase polymerase chain reaction. This could represent an unexpected and yet unexplored gold mine of potential biomarkers predictive of survival or response to therapy.

LncRNAs might also be useful as therapeutic agents. The small size of miRNAs offers an intrinsic advantage in their use as therapeutic bullets by *in vivo* administration.[181] However, because lincRNAs are much longer than miRNAs, they could not be used directly as

therapeutic bullets but would require gene therapy delivery systems (for example, viruses), which would carry potential risks. On the other hand, lncRNAs could be targeted with synthetic siRNAs or miRNAs. Another way to target lncRNAs would be with drugs designed specifically to interact with lncRNAs, as vault RNAs naturally do. Vault RNAs belong to the largest ribonucleoprotein complex in eukaryotic cells (that is, vault), and they are involved in multidrug resistance.[182] Gopinath *et al.* showed that vault RNAs directly bind to chemotherapeutic agents, indicating that it would also be possible to design small molecules that interact with lncRNAs. Of course, vault RNAs are technically short RNAs, ranging from 80 to 90 nucleotides; however, examples of longer RNAs involved with drug interaction exist, such as aptamers.[183–186]

Targeting transcripts the size of lncRNAs may seem like a daunting task, but there is a precedent for fragmenting large ribonucleoprotein complexes into more manageable sizes. This strategy has been applied in the design of ligands that can bind to expanded rCUG and rCAG repeat RNAs that are expressed in myotonic dystrophy type 1 and interact with the Muscleblind-like 1 protein.[187] Moreover, systematic evolution of ligands by exponential enrichment (SELEX) approach can be used to identify chemicals that interact with lncRNAs.[160]

As well as being potential markers or therapeutic targets, lncRNAs could be used as models to develop novel strategies to target tumor cells. For example, synthetic RNA molecules that form hairpin structures simulating DNA transcription factor-binding elements can be generated to target and regulate transcription factor activity as GAS5 does.[164] Synthetic lncRNAs that contain mutant miRNA-binding sites can sequester and reduce expression levels of miRNAs, as it happens in plants.[163]

Finally, small molecule compounds could be used to target lncRNAs. Indeed, small molecule compounds have already been tested for other uses in clinical trials to determine toxicity, body distribution and pharmacokinetics, and in some cases, their use in humans is already approved by the US Food and Drug Administration. Their use with lncRNAs requires only identifying, either by *in silico* predictions or by large library screens, the small molecules that target lncRNA or ribonucleoprotein complexes. If such compounds exist, the transition time from lab to clinic would be very short, which would be good news not only for scientists, but especially for patients with cancers and other diseases.

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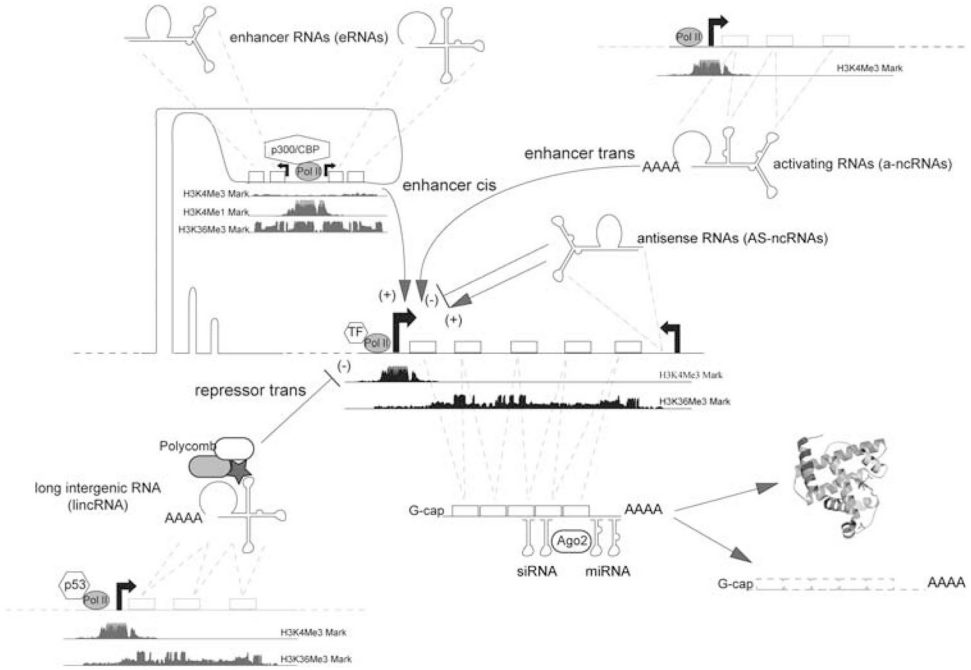

Figure 1.

LncRNA categories and functions. Several classes and functions of lncRNAs are depicted. The main function of lncRNA seems so far to regulate PCG transcription; indeed, lncRNA can either enhance or repress PCG transcription by changes in the chromatin state of the PCGs (for example, by histone methylating or acetylating). Enhancer RNAs derive from transcription of enhancer elements that can be located several kilobases upstream of target genes. Enhancer DNA can both regulate gene expression by DNA looping and direct DNA–DNA interaction with the target promoter, and they also transcribe non-polyA RNAs (that is, eRNA). The function and the role of eRNAs is at this moment unknown. Overall, both long ncRNAs (lincRNA, a-ncRNAs and AS-ncRNAs) and small ncRNAs (for example, siRNA and miRNA) regulate transcription and post transcription steps of protein synthesis, respectively. At the bottom of coding and non-coding transcription units that are shown in picture, the reader can find the peak diagram for CHIP-seq experiments concerning histone modifications: H3K4Me1, mono methylation at lysine 4 of histone 3 (often found near regulatory elements); H3K4Me3, tri methylation at lysine 4 of histone 3 (often found near promoters); H3K36Me3, tri methylation at lysine 36 of histone 3 (often found near active transcripts).

Table 1

Public ncRNA databases

Website (reference)	Name	Species	MicroRNA	Small nucleolar RNA	Infrastructural RNA (ribosomal RNA, transfer RNA, small nuclear RNA)	Notes
http://biobases.ibch.poznan.pl/ncRNA/		Multiple kingdoms	Excluded	Excluded	Excluded	
http://www.noncode.org/ [20]	Noncode	Multiple kingdoms	Included	Included	Small nuclear RNA excluded	Experiment-based, ncRNAs divided on the basis of function (pf classes) and disease association
http://research.imb.uq.edu.au/rnadb/ [21]	Rnadb	Multiple kingdoms	Included	Included	Excluded	
http://www.ncrna.org/ [22]	fRNA	Multiple kingdoms	Included			Functional ncRNA catalog, microarray info about ncRNA, dedicated UCSC page
http://escience.invitrogen.com/ncRNA/		Human, mouse	Excluded	Excluded	Excluded	
http://rnaqueen.sysu.edu.cn/ncRNAimprint/ [23]	ncRNA imprint	Mammals	Included	Included	Excluded	Focused only on imprinting ncRNAs
http://jsm-research.imb.uq.edu.au/nred/cgi-bin/ncrnadb.pl [24]	NRED	Human, mouse	Excluded	Excluded		Expression data
http://www.lncrnadb.org/ [25]	lncRNAdb	Multiple kingdoms	Excluded	Excluded	Excluded	
http://rfam.sanger.ac.uk/ [26]	Rfam	Multiple kingdoms	Included	Included		

Abbreviations: fRNA, functional RNA; lncRNA, long non-coding RNA; ncRNA, non-protein-coding RNA; UCSC, University of California Santa Cruz. The website, reference and content are listed for each database, along with the most interesting feature of each website.

Table 2

lncRNAs that have been or might be (*) linked to cancer

lncRNA	Molecular mechanism	Tumor	Reference	Genome position	Website
aHIF	Messenger RNA decay	Multiple cancers	28–30	hg19 chr14:61,283,843–61,285,036	Noncode
Air	Epigenetic regulation	*	31	NA	lncRNAdb
ak023948	Unknown	Papillary thyroid carcinoma	32	hg18 chr8:134136386-134139194	lncRNAdb
alpha 250/alpha 280	Antisense, transcription regulation	*	33,34	hg19 chr5:149,828,969-149,829,248	lncRNAdb
anril	Antisense, transcription regulation	Prostate cancer	35,36	hg18 chr9:21,984,790-22,111,091	lncRNAdb
anti-NOS2A	NA	Central nervous system tumors	37	hg18 chr17:57,692,139-57,696,081	lncRNAdb
antisense tgf beta 3	NA	*	38,39	NA	lncRNAdb
BA318C17.1	NA	Colon cancer	40	hg19 chr20:14,864,899-14,910,132	Rnadb
bc200	Protein binding	Multiple cancers	41,42	hg19 chr2:47,562,454-47,562,653	lncRNAdb
car intergenic 10	Regulation of gene expression	*	43	hg18 chr10:127,690,946-127,693,326	lncRNAdb
ccnd1-associated ncrnas	Regulation of gene expression	*	44,45	hg19 chr11:69,453,875-69,455,874	lncRNAdb
dhfr upstream transcripts	Regulation of gene expression	*	46	hg18 chr5:79,985,935-79,986,521	lncRNAdb
e2f4 antisense	NA	*	47	NA	lncRNAdb
emx2os	Antisense-sense pairing Dicer1	*	48–50	hg18 chr10:119,233,794-119,294,569	lncRNAdb
gas5	Decoy of glucorticoid receptor	Breast cancer	51	hg18 chr1:172,099,662-172,103,748	lncRNAdb
GNAS1-as RNA	NA	*	52–56	hg19 chr20:57,393,804-57,425,958	Noncode
h19	Transcription regulation (contains miR-675)	Multiple cancers	57–59	hg18 chr11:1,972,982-1,975,641	lncRNAdb
h19 antisense	Regulation of gene expression	*	60	NA	lncRNAdb
h19 upstream conserved 1 and 2	NA	*	61	NA	lncRNAdb
His-1 RNA	NA	*	62,63	hg19 chr2:145,456,944-145,465,439	Noncode
HOTAIR	Epigenetic regulation	Multiple cancers	64–66	hg18 chr12:52,642,363-52,648,782	lncRNAdb
hotairm1	NA	*	67–69	hg18 chr7:27,102,268-27,106,109	lncRNAdb
Hoxa11 antisense	NA	*	70–73	hg19 chr7:27,225,048-27,228,956	Noncode
hoxd3as	NA	*	74,75	NA	lncRNAdb
HULC	Micro RNA decoy	Multiple cancers	76–78	hg18 chr6:8,597,441-8,599,080	lncRNAdb
krasp1	Micro RNA decoy	Prostate cancer	14	hg18 chr6:54,743,128-54,743,996	lncRNAdb
KvlQT1-AS (Kcnq1ot1)	DNMT1 interaction and transcription gene silencing	Colon cancer	79	hg19 chr11:2,465,330-2,870,445	Noncode
LEU2	Pri-micro RNA, other	Chronic lymphocytic leukemia	80	hg19 chr13:50,556,688-50,699,677	lncRNAdb
LOC285194	NA	Osteosarcoma	81	hg18 chr3:117,911,325-117,918,575	lncRNAdb

lncRNA	Molecular mechanism	Tumor	Reference	Genome position	Website
LUST	RNA–RNA interaction, RNA splicing	*	19	hg18 chr3:50,112,040-50,113,425	lncRNAdb
MALAT-1 (NEAT2)	RNA splicing, small RNA production, protein interaction	Multiple cancers	82–84	hg18 chr11:65,021,809-65,030,513	lncRNAdb
MEG3	NA	Multiple cancers	85,86	hg18 chr14:100,362,198-100,397,121	lncRNAdb
MER11C	RNA–protein interaction, regulation of gene expression	Cell lines	83	hg18 chr11:50,410,308-50,411,367	lncRNAdb
Msx1 antisense	NA	*	87–90	NA	Noncode
ncR-uPAR	RNA–protein interaction	*	18	hg18 chr5:76,043,519-76,044,442	lncRNAdb
NCRMS	NA	*	91	hg19 chr12:97,886,239-97,954,478	Noncode
NDM29	NA	Neuroblastoma	92	hg18 chr11:8,917,158-8,917,288	lncRNAdb
NEAT1/TncRNA	RNA nuclear export, paraspeckle organization	*	93–96	hg18 chr11:64,946,845-64,950,577	lncRNAdb
Nkx2.2AS	NA	*	97,98	NA	lncRNAdb
NRON	NFAT nuclear trafficking, RNA-protein binding	*	99,100	NA	lncRNAdb
NSCLC B2	NA	*	101,102	hg19 chr6:11,192,694-11,205,944	Rnadb
NTT sense/antisense	NA	*	103,104	hg19 chr6:136,265,389-136,282,959	Noncode
p53 mRNA	RNA protein binding	Multiple cancers	12	hg19 chr17:7571720-7590863	lncRNAdb
p53int1	NA	*	105	hg19 chr17:7,588,578-7,589,689	Rnadb
PCA3/DD3	NA	Prostate cancer	106	hg18 chr9:78,569,172-78,592,305	Noncode
PCGEM1	NA	Prostate cancer	107	hg18 chr2:193,322,816-193,349,870	Noncode
PCNA-AS	NA	*	108	hg19 chr20:5,100,232-5,100,615	Rnadb
PINC	NA	*	109	NA	lncRNAdb
PR Antisense	Regulation of gene expression	*	110	hg18 chr11:100,505,018-100,574,851	lncRNAdb
PRINS	NA	*	111,112	hg18 chr10:24,576,060-24,584,981	lncRNAdb
PTENP1	Micro RNA decoy	Prostate cancer	14	hg18 chr9:33,663,502-33,667,418	lncRNAdb
RMRP	Mitochondrial RNA processing endoribonuclease, hTERT-dependent small interfering RNA pathway	Leukemia and lymphoma	113,114	hg19 chr9:35,657,750-35,658,014	Rnadb
RPS6KA2 antisense transcript	NA	Cell lines	115	NA	lncRNAdb
saf	NA	Cell lines	116	hg19 chr10:90,751,179-90,752,732	Rnadb
SRA RNA	RNA-protein binding, transcription factor co-activator	Breast cancer	117,118	hg19 chr5:139,930,090-139,937,036	Noncode
TERC	Telomere template	Multiple cancers	119	hg19 chr3:169,481,881-169,483,646	Noncode
terra	Telomerase regulation	Multiple cancers	120,121	NA	lncRNAdb
tie-1AS	RNA–RNA interaction	*	122–124	NA	lncRNAdb
Tsix	Antisense of Xist	*	125,126	hg18 chrX:72,928,765-72,965,791	lncRNAdb
UBE3A antisense	NA	*	127,128	hg19 chr15:25,264,182-25,299,063	Noncode

lncRNA	Molecular mechanism	Tumor	Reference	Genome position	Website
uca1	NA	Bladder cancer	129,130	hg19 chr19:15,939,757-15,946,226	Rnadb
WT1-AS	NA	*	131	hg18 chr11:32,413,861-32,418,212	lncRNAdb
xist	X inactivation	Multiple cancers	125,132–134	hg19 chrX:73,043,280-73,072,588	Noncode
Zeb2NAT	NA	*	135,136	hg18 chr2:144,992,452-144,995,153	lncRNAdb
Zfas1	NA	Breast cancer	137	hg19 chr20:47,894,715-47,905,797	lncRNAdb

Abbreviations: lncRNA, long non-protein coding RNA; NA, not available. For each lncRNA, the name, function, tumor model in which it has been evaluated, and genomic position are listed, along with the public website where each lncRNA can be found.