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REVIEW

Long non-coding RNA: Functional agent for disease traits

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ABSTRACT

In recent years, long non-coding RNAs (lncRNAs) have attracted the attention of researchers with their involvement in all facets of life. LncRNAs are transcripts of more than 200 nucleotides which lack defined protein coding potential. Although they do not code for proteins, a large number of them are involved in regulating gene expression and translation. The presence of numerous lncRNAs in the human genome has prompted us to investigate the contribution of these molecules to human biology and medicine. In this review, we present the potential role of lncRNAs interlinked to different human diseases and genetic disorders. We also describe their role in cellular differentiation and aging and discuss their potential importance as biomarkers and as therapeutic agents.

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Introduction

The notion that most RNAs act as an intermediate message between DNA and protein has been questioned by the discoveries of new roles for RNAs. It is estimated that > 90 % of the human genome undergoes transcription, however only 2 % of it codes for proteins.[1] This results in a large number of RNAs, which do not get translated into proteins. This non-protein coding portion of the genome can be arranged in a variety of categories of non-coding RNAs including transfer RNA (tRNA), ribosomal RNA (rRNA), small nucleolar RNA (snoRNAs), microRNA (miRNAs), small interfering RNA (siRNA), repeat associated siRNA (rasiRNAs) and *piwi* interacting RNA (piRNAs).[2] Although non-coding transcripts such as tRNAs, rRNAs, and spliceosomal RNAs have a wide range of functions and are critical components of cellular machinery, the existence of large pool of non-coding RNAs was initially assumed to be transcriptional noise.[3,4] However, mounting evidences have shown that various non-coding RNAs are involved in discrete cellular functions and participate in different regulatory pathways, including chromosomal architecture, in cellular development and differentiation. With the recent advancement in transcriptomic studies, a new class of non-coding RNAs, long non-coding RNAs (lncRNAs) has attracted the focus of scientific community. Many of these lncRNAs have been shown to play specific roles in normal cell functions and diseases.[4]

In this review, we focus on lncRNAs and discuss their role in pathophysiology of different diseases, and the medical implications of the use of lncRNAs as diagnostic biomarkers or as the basis for novel therapies.

Long non-coding RNA

H19 and *Xist* are among the first characterized lncRNAs.[5,6] Since then, a large number of studies involving DNA tiling arrays,[7] next-generation sequencing,[8] and transcriptomic studies[9-11] have identified thousands of lncRNAs that have been cataloged in various databases such as NONCODE, GENCODE and lncRNAdb.[12-14] LncRNAs are generally defined as RNA transcripts with more than 200 nucleotides lacking a clear open reading frame.[15] However, some ncRNAs smaller than 200 nucleotides such as BC1 and snaR have been classified in some studies as lncRNAs.[14] Additionally, some lncRNAs e.g. lncRNA *pncr003:2L* in *Drosophila* are known to code small proteins and peptides.[16,17] Since the size definition is purely based on conventional threshold of RNA purification techniques and has no biochemical, structural or functional basis, an alternative definition of lncRNAs has been proposed as ncRNAs that function either as primary or spliced transcripts, independent of existing known classes of small ncRNAs.[14] In recent years, there has been dramatic rise in discovery of lncRNAs. To assist in interpreting their function, lncRNAs have been classified based on their length, genomic location of their transcription, association with other functional DNA elements and their subcellular localization.[18,19] The simplest classification of lncRNAs is based on their transcription site relative to other genes with different classes described below.

Intergenic lncRNAs and intronic lncRNAs

The transcription sites for intergenic lncRNAs (also called as lincRNAs: long intergenic non-coding RNAs) are located

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between 2 non-overlapping protein-coding genes. On the other hand, intronic lncRNAs are lncRNAs whose transcripts arise from introns of protein-coding genes.

Sense and antisense lncRNAs

Nearly 70 % of sense transcripts have been reported to have complimentary antisense transcripts.[20] Transcription of sense lncRNAs occurs from the same strand of genes that code for protein. These may cover the whole genes or only a fraction of the genes. Antisense lncRNAs (also called as natural antisense transcripts; NAT) are transcribed from the antisense strand overlapping with exonic or intronic region of protein coding genes or cover the entire gene sequence through the introns.

Enhancer and promoter associated lncRNAs

LncRNAs transcribed starting at enhancers are termed enhancer ncRNAs (eRNA). These lncRNAs are involved in forming chromatin loops with promoters that then promotes transcription initiation.[21] Transcription of promoter associated lncRNAs (PALR) overlaps the 5′-end of protein coding region comprising the promoter region and first exon or intron.[22]

Functions of long non-coding RNA

LncRNAs play critical roles in regulation of protein coding genes,[23] stem cell pluripotency and differentiation,[24] allelic expression,[25] cell cycle control,[26] apoptosis and senescence.[27] LncRNAs can be present in nucleus, cytoplasm and also in mitochondria.[28,29] LncRNAs present in different subcellular locations regulate expression of protein coding genes via different mechanisms e.g., controlling chromatin modification, transcription, and translation.

Chromatin modification

In mammalian cells, tissue specific gene expression is controlled by DNA or chromatin modifications. These modifications are performed by a limited number of enzymes (DNA methyltransferases, histone methyltransferases, acetylases, deacetylases etc.) and chromatin-modifying complexes (Polycomb-group and Trithorax-group), many of which lack affinity for particular DNA sequences.[30] Various non-coding RNAs including lncRNAs form a network of epigenetic modulators by providing platforms for assembly of these enzymes and chromatin remodeling complexes and guiding them to specific genomic sites (Fig. 1A).[31] For example, the HOX transcript antisense RNA (*HOTAIR*), an lncRNA transcribed from the *HOXC* locus interacts with polycomb chromatin remodeling complex PRC2 to induce a repressive chromatin state by silencing transcription across 40 kb of the *HOXD* locus in *trans*.[15] LncRNAs have also been shown to activate transcription by recruiting chromatin-modifying complexes like H3K4 trimethyltransferase MLL1 complex and by activating specific enhancer regions by changing 3-D chromatin conformation.[32]

Transcriptional regulation

Different cells experience widespread transcription initiation at enhancers and promoters, however, protein expression takes place in tissue specific manner predicting a major role for lncRNAs associated with these regions (eRNA and PALR) (Fig. 1B).[23,33] LncRNAs transcribed from the promoter regions may recruit RNA binding proteins and regulate their function during transcription.[34] For example, expression of lncRNAs associated with the cyclin D1 gene promoter is induced by DNA damage signals. Here, lncRNAs act cooperatively to control the activity of RNA binding protein TLS that eventually hinders the histone acetyltransferase activities of CReB binding protein and p300 to silence the expression of cyclin D1.[34] The ability of lncRNAs to employ RNA binding proteins to gene promoters greatly increases the transcriptional regulatory machinery.[34] LncRNAs also act as co-factors to control activity of transcription factors. In mice, the lncRNA *Evf2* transcribed from a conserved distal enhancer controls the binding and action of the transcription factor D1X2 to this enhancer resulting in up-regulation of adjacent protein-coding genes.[35]

Post-transcriptional regulation

Many genes express antisense lncRNAs, which can overlap with key elements in mRNA to regulate various steps in mRNA processing (Fig. 1C).[36] For example, an intron in the 5′ untranslated region of the zinc finger Hox mRNA *Zeb2* contains an internal site for ribosome entry, which is required for systematic translation of Zeb2 protein. Antisense lncRNA *Zeb2NAT* overlaps 5′ splice site of this intron, thus preventing its splicing by spliceosomes leading to accumulation of Zeb2.[37]

LncRNAs can also inhibit the expression of some specific proteins by forming RNA duplex with the mRNAs.[38] Annealing of lncRNA can target protein effecter complexes to the mRNA transcript in a way similar to the targeting done by the RNA-induced silencing complex (RISC) to mRNAs by siRNAs. For example, to achieve X-chromosome inactivation, lncRNAs *Xist* and *Tsix* form an RNA duplex which is processed to small RNAs in Dicer dependant manner.[38] Some lncRNAs can also act as precursor for miRNAs, e.g. H19/miR-675.[39]

Medical implications

LncRNAs have versatile contributions to various cellular functions. Mutations or aberrant expressions of lncRNAs may result in cellular dysfunction leading to disease state. Genome-wide association studies (GWAS) have revealed that a large number (88%) of disease associated SNPs reside outside protein coding sequences.[40] Of these, 45% SNPs belong to intronic region and 43% SNPs belong to intergenic region of human genome. Many recent studies have implicated lncRNAs in the pathogenesis of various other diseases like Alzheimer's disease, Huntington's disease, psoriasis, diabetes and cardiovascular diseases.[41-44] The emerging roles of lncRNAs in diverse disease conditions have paved a new arena to design novel diagnostics and therapeutics. Comparative profiling of lncRNAs isolated from different body fluids such as serum, plasma, urine or sputum can serve as a potential method for early detection of various diseases. For

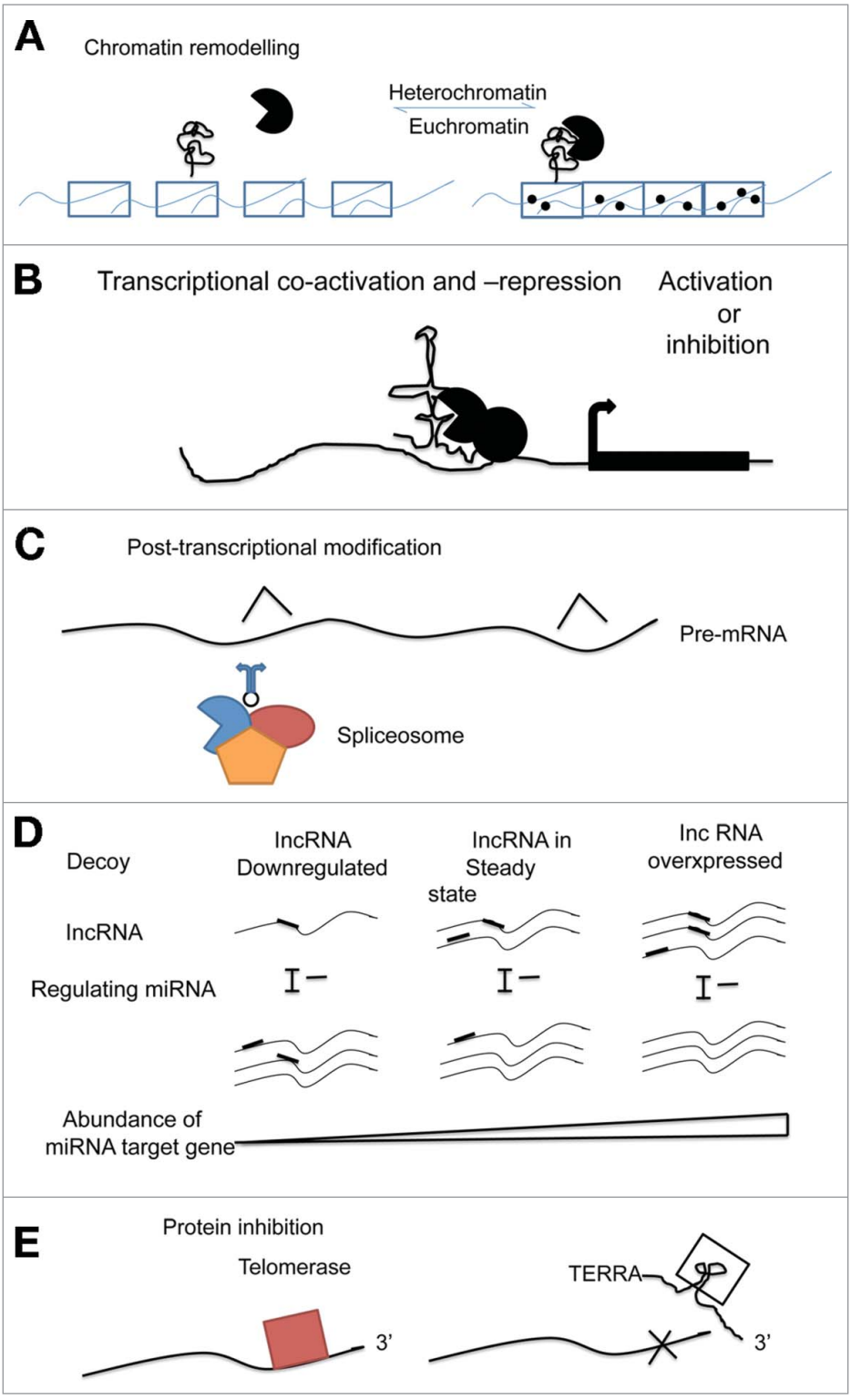

Figure 1. Different mechanisms of functions associated with lncRNAs. They serve in (A) Chromatin modulation, (B) Transcriptional activation and suppression, (C) as post transcriptional machinery, (D) miRNA decoy element and (E) as protein inhibitor (Modified from Cheetham et al. 2013 Br J Cancer, 108:2419-25).

example, identification of lncRNA *PCA3* in urine is being used for clinical detection of prostate cancer.[45]

The current strategies to treat diseases mostly rely on inhibitory drugs. However, to treat certain diseases upregulation of gene expression would be desirable. For example, certain neurological disorders in early stages can be treated with elevated expression of neuro-protective growth factors. In such cases, lncRNAs provide excellent targets for therapeutic agents.[46] In the following sections of this review, we will describe what is known about the orchestrating role of lncRNAs in disease pathogenesis, diagnosis and their potential as therapeutic agents and targets.

Development and endocrine glands

LncRNAs play important roles in normal endocrine physiology and development (Table 1) (Fig. 2).[47] Several studies have

Table 1. LncRNAs expressed in various endocrine tissues. The list represents lncRNAs involved in endocrine function and diseases. Other lncRNAs that are involved in cancer of these tissues are listed in Table 2.

Organ	lncRNA	Function	Disease association	Ref.
Mammary Gland	*Pinc* Family	Lobuloalveolar differentiation	-	57
Adipose Tissue	*Sra1*	Activates PPARγ to induce adipogenesis	Obesity	56
	lncRAP Family	Adipogenesis	Obesity	55
	Blnc1	Thermogenic adipocyte differentiation	-	122
	PU.1 AS	Blocks translation of *PU.1* mRNA and promotes adipocyte differentiation	Obesity	123
	naPINK1	Inhibits expression of *PINK1* leading to mitochondrial dysfunction	Obesity, Diabetes	51
Adrenal Gland	*SRA1*	Regulates steroidogenesis	-	60
Pancreas	*ANRIL*	Controls expression of *Cdkn2a* and promotes β-cell proliferation	Diabetes	49
	HI-LNC25	Regulates level of *GLIS3* mRNA	Diabetes	42
	KCNQ1OT1	Regulates expression of *CDKN1C* that controls islet proliferation	Diabetes	124
	H19	Regulates expression of *IGF2*	Gestational Diabetes	125
	MEG3	Unknown	Diabetes	126
Pineal Gland	*lncSN* family	Regulates circadian rhythm	-	59

demonstrated the role of lncRNAs in pancreatic β-cell physiology and diabetes.[42,48] Transcriptome analysis of human pancreatic β-cells revealed a total of 1128 lncRNAs, some of which showed higher expression on addition of glucose to the β-cell culture. One of these lncRNAs, *HI-LNC25* controls the expression of *GLIS3* that encodes a transcription factor and regulates expression of insulin and other islet specific transcription factors.[42] Comparative analysis of transcriptomes of individuals with and without type-2 diabetes mellitus (T2DM) revealed 493 lncRNAs of which 54 lncRNAs showed expression level correlated to the levels of HbA_{1c}, indicating a direct association with the disease status.[48] The regenerative capacity of β-cells in mouse pancreas decreases with age due to up-regulation of the *Cdkn2a* locus. The lncRNA *ANRIL* (Antisense Non-coding RNA in the INK4 Locus) is involved in regulation of glucose homeostasis in adult mice by suppressing the expression of *Cdkn2a* locus that promotes cell division of pancreatic β-cells.[49,50] Other lncRNAs that may be involved in T2DM are *naPINK1* and *KCNQ1OT1* (See Table 1).[51,52]

Adipose tissues release a number of chemicals including leptin, which regulates appetite and adiponectin, which helps in regulating various metabolic processes such as glucose metabolism and fatty acid oxidation.[53,54] In a recent study, a sum of 175 lncRNAs showed differential expression during adipogenesis. Among them, a group of 10 lncRNAs, named as *lncRAP 1–10*, were shown to have the capacity to bind the adipogenic transcription factors PPARγ and C/EBPα, and seemed to be required for proper adipocyte differentiation.[55] Another lncRNA steroid receptor RNA activator 1 (*Sra1*) binds and coactivates PPARγ in mice. The mice knock-out for *Sra1* locus showed resistance to develop obesity and glucose intolerance with high-fat diet.[56]

During pregnancy, mammary glands are expanded under the control of hormones estrogen and progesterone. The lncRNA *Gb7* or *Pinc* (Pregnancy induced non-coding RNA) is persistently up-regulated after treatment with estrogen and progesterone in rats. The spliced variants of *Pinc, mPinc1.0* and *mPinc1.6*, show over-expression in the lobulo-alveolar structure of mammary glands during pregnancy, repressed during

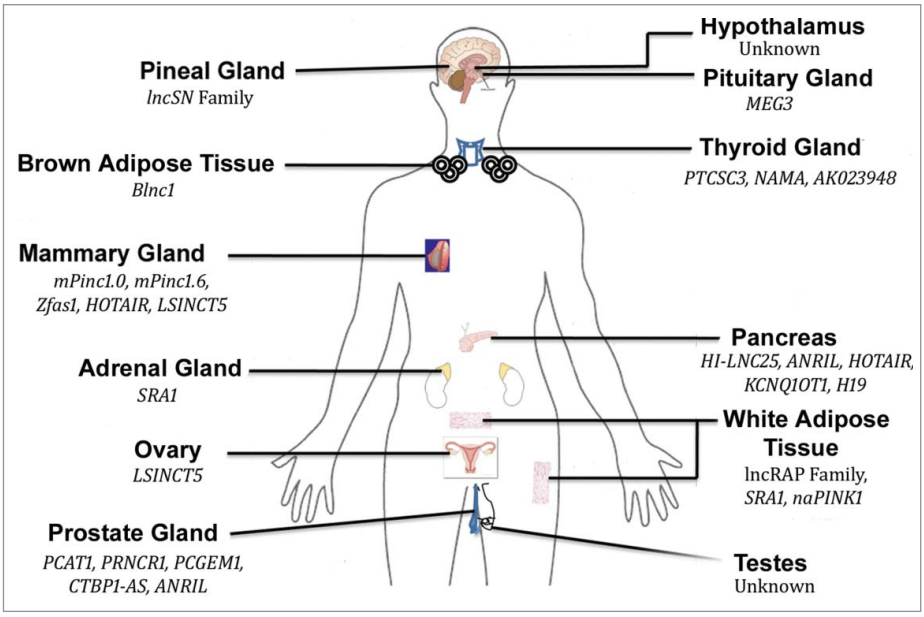

Figure 2. LncRNAs secreted from various endocrine tissues. Tissues are labeled in bold and the involved lncRNAs are also noted. (Modified from Knoll et al. 2015 Nat Rev Endocrinol, 11:151–60)[47].

lactation and again upregulated after involution.[57] The interaction of *mPinc* with PRC2 suggests a role in maintaining repressive chromatin state. In mice, another lncRNA zinc finger antisense 1 (*Zfas1*) shows down-regulation between pregnancy and lactation and upregulation during lactation and involution. *Zfas1* also serves as tumor suppressor and a potent biomarker for breast cancer.[58]

Pineal gland regulates circadian rhythm by secreting melatonin in accordance with the season and time of day. The tissues from the pineal gland in rat express 112 lncRNAs referred to as lncSNs (lncRNAs, Section on Neuroendocrinology) whose expression oscillates throughout the day. A large fraction (59%) of lncSNs showed higher expression during night.[59] In depth analysis of 8 lncSNs showed that their expression was regulated in the suprachiasmatic nuclei of neurons, patterns that were continued in constant darkness indicating their circadian nature.

In adrenal glands, the nuclear receptor NR0B1 coactivates or corepresses another nuclear receptor Steroidogenic factor 1 (SF-1) in a dosage dependent manner.[60] The coactivation of SF-1 by NR0B1 is enhanced by non-coding RNA steroid receptor RNA activator (*SRA*) resulting in activated expression of melanocortin 2 receptor (MC2R) (also known as adreno-corticotropin hormone (ACTH) receptor). The knockdown of *SRA1*, a variant of SRA in human adrenocortical cells resulted in reduced expression of steroidogenic acute regulatory protein (StAR) and MC2R suggesting a role for the lncRNA *SRA* in steroidogenesis and adrenal function.[60]

Besides their roles in maintaining development and physiology of endocrine glands, many lncRNAs are involved in cancer of endocrine glands.[47] The lncRNA *HOTAIR* and long stress induced non-coding RNAs (LSINCTs) show overexpression in breast cancer. The lncRNA *MEG3* is a tumor suppressor expressed in pituitary glands. LncRNAs *PTCSC3, NAMA* and *AK023948* show deregulation in thyroid cancers. Two lncRNAs, *PCGEM1* and *PRNCR1*, show over-expression in prostate cancer. *PCAT1*, a member of a group of 121 lncRNAs identified as prostate cancer associated lncRNA transcripts (PCATs), functions as a transcriptional suppressor in complex with PRC2 leading to inhibition of various tumor suppressor factors such as *BRCA2, CENPE* and *CENPF*.[47]

Cardiovascular disease

Recent studies have shown the influence of lncRNAs in the development of the fetal heart, which involves precise control of gene expression to guide differentiation from pluripotent cells into mesodermal and cardiac cell types. Besides specific proteins, a large number of non-coding RNAs play a part in cellular differentiation. Tissue specific expression of the lncRNAs, Braveheart (*Bvht*) and Fendrr are associated with early development of the heart in mouse.[61,62] These lncRNAs in association with PRC2 regulate expression of genes involved in cardiogenesis. They also control the activity of various transcription factors for mesodermal differentiation.[43] Although lncRNAs were initially thought to be non-protein coding sequences, some of them do encode small functional peptides.[17] In *Drosophila*, lncRNA *pncr003:2L* is translated into 2 polypeptides sarcolamban A and B with 28 and 29 amino acid residues, respectively. These peptides share conserved sequences and structures in different species including humans. These peptides regulate Ca^{2+} uptake by SERCA2, thereby influencing muscle contraction in heart.[16] Mutations in these lncRNAs result in congenital cardiac diseases.

Besides contributing to cardiogenesis, non-coding RNAs are involved in various cardiovascular disorders. A number of GWAS have linked cardiovascular diseases with SNPs in non-coding regions in human genome.[63-65] The lncRNA *ANRIL* located at chromosome 9p21 is associated with a GWAS hotspot for age related diseases such as Alzheimer's disease, coronary disease, type 2 diabetes, endometriosis, glaucoma and cancer.[66,67] *ANRIL* transcription takes place in coronary smooth muscle cells, vascular endothelial cells, and monocyte derived macrophages. The transcript levels of elevated expression of *ANRIL* are directly correlated to the severity of atherosclerosis.[68] Myocardial infarction-associated transcript (*MIAT*), a 9 kb long lincRNA is expressed in the nuclei of developing neural cells and has also been implicated in retinal cell fate specification. Several variants of *MIAT* are associated with higher susceptibility to myocardial infarction.[69] A SNP (exon 5 11,741 G >A) in *MIAT* region allows enhanced transcription of this lincRNA. A *MIAT* variant that has been implicated in splicing regulation shows higher expression in retinal cells in diabetes. Knocking down *MIAT* led to improvement in retinal microvascular dysfunction caused by diabetes mellitus.[70] These results showed that *MIAT* is involved in pathological angiogenesis and represents a therapeutic target against neovascular diseases.

The involvement of miRNAs in regulation of cardiac specification and differentiation has been well studied. LncRNAs may serve as decoy or competitive endogenous RNAs (ceRNAs) for miRNAs and thus indirectly regulating gene expression (Fig. 1D).[71] A recent study showed that a small non-coding RNA miR-489 targets the myeloid differentiation primary response gene 88 (Myd88) to antagonize cardiac hypertrophy.[71] The cardiac hypertrophy related factor (*CHRF*) acts as a ceRNA for miR-489 leading to up-regulation of Myd88 and thereby cardiac hypertrophy.

Although circulatory lncRNAs have been used as a biomarker for cancer; the utility of lncRNAs as biomarkers for cardiovascular diseases is largely unknown. Kumarswamy et al. (2014) found an association between an lncRNA and heart disease.[72] They discovered differential regulation of the mitochondrial lncRNA *uc022bqs.1* (LIPCAR) at different stages of myocardial infarction in plasma of patients as compared to healthy subjects. With the large number of lncRNAs expressed in human genome, the possibility to identify new biomarkers for the diagnosis of cardiovascular diseases is wide open.

Cell differentiation, apoptosis and cancer

Research in recent years has revealed a major contribution of lncRNAs to almost all phases of life. They are involved in regulating cell cycle, cellular differentiation and cell death. Different environmental changes, stresses, infections, life style changes and aging influence the delicate balance of various biomolecules in the cell leading to perturbed cellular physiology and disease. Cancer is a disease of disturbed cellular division and death. Several lncRNAs have been implicated in the cancer

Table 2. LncRNAs associated with carcinogenesis.

LncRNA	Disease association	Function in Oncogenesis	Functional mechanism	Ref.
UCA1	Bladder cancer	Oncogene/ Biomarker	Promotes cell proliferation and metastasis	86,127
GAS5	Breast cancer	Tumor suppressor	inhibits expression of glucocorticoid receptor, induces apoptosis	128
Zfas1	Breast cancer	Tumor suppressor	Regulates alveolar development and epithelial cell differentiation	58
KCNQ1OT1	Colorectal cancer	Unknown	Imprinting defects	129
linc-p21	Colorectal cancer	Tumor suppressor	hnRNP-K mediated gene repression	80
PTENP1	Hepatocellular carcinoma	Tumor suppressor	decoy oncomirs targeting PTEN	130
aHIF	Multiple cancer	Biomarker	Unknown	131
ANRIL	Multiple cancer	Oncogene	Inhibits the expression of tumor suppressor genes	132
H19	Multiple cancer	Tumor suppressor	controls expression of multiple genes involved in growth, proliferation and apoptosis	133
HOTAIR	Multiple cancer	Oncogene	PRC2 mediated methylation of various genes	77
HULC	Multiple cancer	Oncogene/ Biomarker	modulates expression of p18 to inhibit apoptosis	116
MALAT1	Multiple cancer	Oncogene	controls RNA splicing, promotes cellular mobility	74,76
MEG3	Multiple cancer	Tumor suppressor	Inhibits tumor growth	134
PANDA	Multiple Cancer	Oncogene	Regulates apoptosis	81
PCA3	Prostate cancer	Biomarker	Silencing expression of tumor suppressor gene PRUNE2	45,135
PCGEM1	Prostate cancer	Oncogene	promotes cell proliferation	85
PRNCR1	Prostate cancer	oncogene	Promotes cancer cell proliferation in association with PCGEM1	136
PCAT1	Prostate Cancer, Hepatocellular carcinoma	Oncogene/ Biomarker	Inhibits expression of tumor suppressor, promotes cell proliferation	137,138
PTCSC3	Thyroid Cancer	Tumor suppressor	Decoy miR-574-5p	139

pathophysiology with some of them providing strong targets as biomarkers for diagnosis of diseases and as therapeutic targets to treat the diseases (Table 2).[73]

MALAT1 is one of the first lncRNAs to be associated with human lung cancer.[74] Since then it has been implicated in the cancer of various other organs including lung, liver, kidney, colon, breast, pancreas, bladder and many more.[75] *MALAT1*, which is involved in control of alternative splicing by modulating the phosphorylation of SR proteins, shows normal expression in various healthy tissues but is up-regulated in cancerous cells. Silencing *MALAT1* results in impaired cellular mobility and hence has been linked with cancer metastasis.[76] The lncRNA *HOTAIR* is highly expressed in various cancerous tissues including liver cancer, breast cancer and colon cancer. Overexpression of *HOTAIR* retargets polycomb repressive complex 2 (PRC2) to new sites in genome including various tumor suppressor genes leading to altered H3K27 methylation, which in turn promotes proliferation and metastasis of cancerous cells (Fig. 3A).[77,78] High levels of *HOTAIR* are associated with relapse for liver carcinoma patients.[79] Similar to *HOTAIR*, lncRNA *ANRIL* is also associated with several cancer types including acute lymphoblastic leukemia, nasopharyngeal carcinoma, glioma, breast cancer and basal cell carcinoma. *ANRIL* over-expression represses the expression of the *INK4B–ARF–INK4A* locus genes containing 3 tumor suppressor genes by recruiting PRC1 and PRC2, resulting in cancer proliferation.[66]

A number of lncRNAs are activated by the tumor suppressor p53 in response to DNA damage (Fig. 3B).[78] The tumor suppressor p53 up-regulates lncRNA *lincRNA-p21* by binding at its promoter. The lncRNA *lincRNA-p21* interacts with heterogeneous nuclear ribonucleoprotein K (hnRNP-K) and represses the expression of multiple genes in the p53 pathway and p53 mediated apoptosis.[80] Another p53 induced lncRNA *PANDA* (P21-associated ncRNA DNA damage activated) down-regulates pro-apoptotic genes by interacting with the transcription factor NF-YA.[81] The lncRNA *H19* and the H19 derived miR-675 are over-expressed in human colorectal cancer cells, whereas they show normal expression in surrounding tissues.[39] LncRNA *H19* regulates the expression of several genes within the imprinted gene network, a cluster of genes whose expression depends on the parent contributing them. These genes, including *H19* itself and insulin like growth factor 2 (*IGF2*), are involved in growth, proliferation and apoptosis. The lncRNA *H19* forms a ribonucleoprotein complex with methyl-CpG–binding domain protein 1 (MBD1), which interacts with histone lysine methyltransferases to induce methylation of ICRs resulting in repression of genes in this locus.[82] Furthermore, downregulation of lncRNA *H19* leads to lower levels of p57 and decreases tumor growth.[83]

Since several lncRNAs are tissue or cell specific and may control the progression of many diseases, they are considered biomarkers for disease diagnosis and as therapeutic targets.[84] The prostate cancer associated lncRNA prostate cancer gene 3 (*PCA3*) is routinely used as a urine test to diagnose prostate cancer risk.[45] LncRNA *PCGEM1* is expressed in a tissue-specific manner in prostate glands and displays enhanced expression in high risk groups.[85] Another cancer related biomarker lncRNA *UCA1* (urothelial carcinoma associated 1), which can be detected in urine, shows high sensitivity and specificity for bladder carcinoma.[86] Other promising biomarkers for different cancer types include *AA174084* found in gastric juice of gastric cancer patients, *MALAT1*- derived fragment detected in plasma of prostate cancer patients, *HULC* in plasma of hepatocellular carcinoma patients.[87-89] In a successful attempt to treat H19-driven cancer cells, a plasmid preparation BC-819 (DTA-H19) that carries the diphtheria toxin under control of the H19 regulatory sequence was used as an intratumoral injection resulting in reduced tumor size.[90] These studies suggest the potential of lncRNAs as biomarkers in cancer diagnosis and targets for treatment.

Immunity and autoimmune diseases

Immunity is the most organized cellular defense of the body against pathogenic agents. It requires correct development, differentiation and activation of immune cells. Th1 helper cells are the major immune cells involved in adaptive immunity against

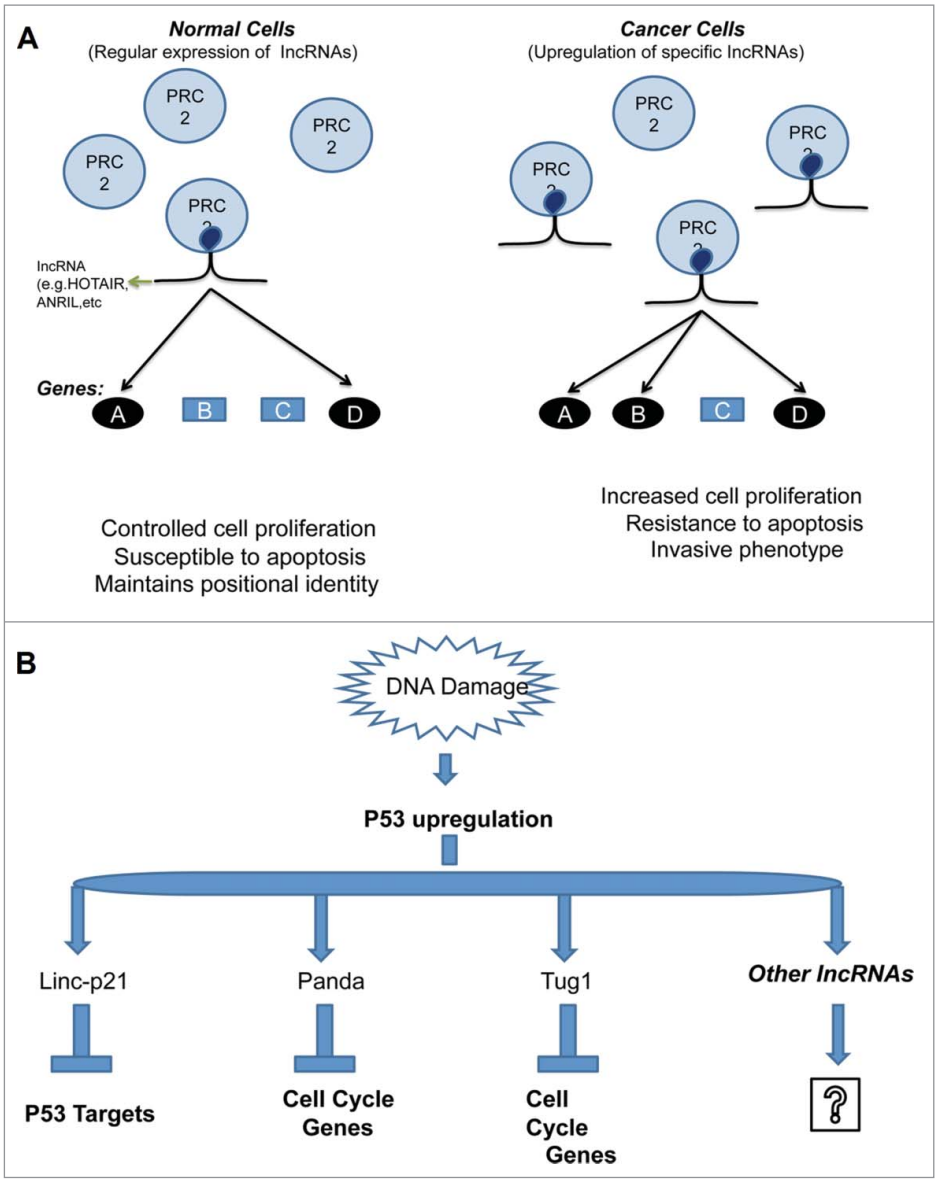

Figure 3. Misexpression of different lncRNAs in cancer that modulate different pathways with diversified mechanisms (A) a group of lncRNAs (e. g. HOTAIR, ANRIL and others) modulate chromatin structure and organization in cis or in trans (PRC2) to alter their expression (B) A group of lncRNAs induced p53 regulated pathway. The lncRNA once activated modulated via different protein partners. (Modified from Niland et al. 2012 Front Genet 3:25)[78].

various pathogens. Hundreds of lncRNAs have been identified in CD8+ T cells from human and mouse spleen suggesting their importance in lymphocyte differentiation and activation.[91] The lincRNA *TMEVPG1* (also named as *NeST*) in CD8+ T-cells has an important role in controlling Theiler's virus infection. *TMEVPG1* along with T cell specific transcription factors T-bet/Stat can up-regulate expression of IFN-γ recruiting H3K4me3 to the *ifng* gene through interaction with the WDR5 subunit of H3K4 methyltransferase.[92] An lncRNA *lncDC*, which is uniquely expressed in dendritic cells, binds with STAT3 signaling molecule in cytoplasm suggesting a role for lncRNAs in direct control of cellular differentiation and function.[93]

B-lymphocytes, originating from bone marrow have function in generating antibodies and presenting pathogenic antigens to other immune cells. In the production of antigen receptors, multiple non-coding RNAs have been implicated in regulating variable, diversity and joining [V(D)J] recombination by bringing V_H region close to DJ_H region.[94,95] Natural killer cells kill virus infected cells and tumors with proteins like perforin and proteases. Cytotoxic activity of these cells is regulated by many cell surface class I MHC receptors, such as killer cell immunoglobulin-like receptor (KIR). Many KIR genes transcribe antisense lncRNAs that in some cases have been shown to reduce the expression of KIR proteins by overlapping with exon 1 and 2 of genes coding those.[96] Macrophages are another class of immune cells that are involved in removal of microbes and other damaged cells from the body by phagocytosis. PTPRJ or CD148, a tyrosine phosphatase with known tumor suppressor activity, is expressed abundantly in macrophages in response to LPS or TLR ligands but down-regulated in response to CSF-1. The lncRNA *ptprj-as1* expressed antisense to the *ptprj* gene and is co-regulated in response to TLR ligands or CSF-1.[97] Another non-coding RNA *lincRNA-Cox2* or *Ptgs2* shows overexpression in dendritic cells after stimulation with TLR4.[98] In a recent study, a total of 159

lncRNAs showed induction or suppression in THP1 macrophages treated with Pam3CSK4 in comparison to their expression in non-treated cells.[99] In particular, the expression of TNF-α was shown to be regulated by lncRNA *linc1992* or *THRIL* (TNFα and hnRNPL Related Immunoregulatory LincRNA) by interacting with the heterogenous nuclear ribonucleoprotein L (hnRNPL) and binding its promoter. Interestingly, *THRIL* has been found to be associated with Kawasaki disease, an acute inflammatory disease of childhood.[99]

Related to the role of non-coding RNAs in regulating the development and activity of different immunological cells, they also have shown their role in various autoimmune diseases (Table 3). Autoimmune thyroid diseases (AITD), Graves' disease and Hashimoto's thyroiditis, are caused by infiltration of the T-cell in the thyroid gland leading to production of anti-thyroid autoantibodies. A SNP Ex9b-SNP10, located in intron 9 of *ZFAT* gene and promoter region of a non-coding transcript small antisense transcript of *ZFAT* (*SAS-ZFAT*), shows association with high risk group of AITD.[100] The T-allele of this SNP results in dysregulated B-cell function by up-regulating *SAS-ZFAT* and down-regulating truncated *ZFAT*.

The hyper-proliferation of keratinocytes in skin of psoriasis patients is induced by infiltrating T-lymphocytes at the dermal-epidermal junction. A non-coding RNA *PRINS* (*P*soriasis susceptibility-related *R*NA gene *In*duced by *S*tress) has been shown to be overexpressed in the psoriatic epidermal cells as compared with healthy skin cells.[101] Similarly, another autoimmune disorder rheumatoid arthritis (RA) is the result of joint destruction due to the action of several proteases secreted by T, B, and APC cells in response to an alteration in the synovial microenvironment by proinflammatory cytokines and chemokines. Expression of 85 lincRNAs in CD14+ monocytes from RA patients is regulated by the proinflammatory chemokines TNF-α and IL-6, and showed significant upregulation due to anti-TNFα or anti-IL6 treatment.[102] Another non-coding RNA *lincRNA-p21* showed reduced expression in RA patients. Treatment of RA patients with methotrexate inhibited the activity of NF-κB by inducing expression of *lincRNA-p21* that is thought to regulate gene expression through hnRNP-K mediated repression.[80,103] Besides these diseases, lncRNAs have also been associated with various other autoimmune diseases such as systemic lupus erythematosus, juvenile idiopathic arthritis, primary biliary cirrhosis, asthma, celiac disease and inflammatory bowel disease.[44,104]

Neurological disorders

The onset and progression of many neurological disorders are affected by dysregulation of lncRNAs and genes that they regulate. The best characterized example of neurological diseases controlled by lncRNAs is Alzheimer's disease (AD). Accumulation of extracellular amyloid-β deposits due to increased expression of 2 proteases, β-secretase or β-Site APP-Cleaving Enzyme 1 (BACE1) and γ-secretase, results in AD pathophysiology. An antisense transcript of *BACE1* (*BACE1-AS*), over-expressed in AD patients, forms a RNA duplex with *BACE1* mRNA to stabilize it resulting in higher level of BACE1 protein.[41] Knocking down *BACE1-AS* resulted in reduced levels of *BACE1-AS* and BACE1 lowering the levels of amyloid-β synthesis and aggregation in brain. Thus, *BACE1-AS* presents a promising therapeutic target to treat AD.[105] In contrast to a gradual decrease in the expression in the healthy aging brain, lncRNA *BCYRN1/BC200* showed up-regulation in brain of patients with age related AD. The level of translational regulator *BCYRN1/BC200* was directly correlated with the severity of the disease.[106] *BC200* RNA interacts with various RNA-binding proteins that are involved in protein synthesis at postsynaptic sites in neurons.[107] Thus, they have role in modulating protein synthesis in dendrites and may contribute to synaptodendritic deterioration in aging brain.

Neurodegenerative disorder spinocerebellar ataxia type 8 (SCA8) that affects muscle and speech coordination is caused by trinucleotide repeats in protein coding gene ataxin 8 (*ATXN8*), with CAG repeats resulting in poly-Q protein, and in an lncRNA gene ataxin 8 opposite strand (*ATXN8OS*) with CUG expansion. The lncRNA *ATXN8OS* interacts with splicing factor MBNL1 in neurons leading to anomalous splicing of GABA-A transporter 4 (*GABT4*) and loss of GABAergic inhibition in the granular cell layer, which is suggested to contribute to the SCA8 phenotype.[108] In another model of SCA8 pathophysiology, the lncRNA *ATXN8OS* was shown to repress the expression of *KLHL1* gene located in close vicinity of *ATXN8*.[109] Reduction in *KLHL1* expression decreases neurite outgrowth during development of neurons resulting in brain dysfunction.

Several other lncRNAs have been linked with different cognitive disorders such as schizophrenia, autism spectrum disorders (ASD), and Angelman syndrome. The lncRNA *MIAT* that interacts with splicing factors QKI and SRSF1 shows down-regulation in brain tissues of schizophrenia patients.[110] The loss of *MIAT* expression was associated with global changes in alternative splicing as observed for *DISC1*, a gene associated with schizophrenia. Microarray analysis of brain tissues from ASD patient revealed 222 differentially expressed lncRNAs. Most of these lncRNAs were colocalized with protein coding genes associated with brain development.[111] Many neurological diseases such as Parkinson's disease, amyolateral sclerosis and AD have defects in

Table 3. LncRNAs involved in immune response.

LncRNA	Cell involved	Functional mechanism	Associated Disease	Ref.
PRINS	Epidermal Cells	Protects cells against stress induced death	Psoriasis	101
LincRNA-p21	THP-1 monocytes	Decreased expression induces activity of NFκB	Rheumatoid arthritis	103
SAS-ZFAT	CD19+ B cells	SNP in SAS-ZFAT promoter region correlates to high risk of autoimmune thyroid disease	Autoimmune thyroid disease	100
NeST	CD8+ T-cells	Regulates expression of IFNγ by methylation through H3K4 methyltransferase	Microbial infection	92
GAS5	T-lymphocytes	Interacts with glucocorticoid receptor and suppresses GR-induced transcriptional activity	Systemic lupus erythematosus	128
THRIL	THP-1 monocytes	Regulates expression of TNFα via hnRNPL	Kawasaki disease	99
Lnc-DC	Dendritic cells	Activates transcription factor STAT3 to support cellular differentiation		93
Ptprj-as1	Macrophage	Expressed in response to lipopolysaccharide		97

mitochondria of the affected neurons, indicating possible role for mitochondrial lncRNAs in neurodegeneration.[112]

Bio-age

Aging is a biological process during which cells, tissues and organs undergo progressive deterioration leading to loss of function, diseases and death. Different lncRNAs are involved in regulation of cellular activity, proliferation, differentiation, quiescence, senescence, stress response and other functions related to aging by modulating gene expression.[27,113] Cellular aging is associated with gradual reduction in the length of telomere, which is controlled by telomerase ribonucleoprotein complex formed by the interaction between protein telomerase reverse transcriptase (TERT) and the lncRNAs *TERC* (telomerase RNA component) and *TERRA* (telomeric repeat-containing RNA) that contains telomeric repeats. *TERC* provide template for synthesis of telomeric repeats to prevent premature aging, whereas *TERRA* suppresses telomeric elongation by inhibiting TERT activity (Fig. 1E). *TERC* downregulation or *TERRA* over-expression are associated with premature aging.[27]

Several epigenetic factors such as DNA methylation, histone modification and heterochromatin formation are involved in the aging process. Several lncRNAs are involved in age related regulation of these epigenetic alterations. LncRNA X-inactive-specific transcript (*XIST*), which is involved in X-chromosome silencing in females, is downregulated in aging cells.[114] The overexpression of insulin-like growth factor 2 receptor (IGF2R) in senescent cells, as compared with proliferating cells, indicates its role in longevity. The lncRNA *Airn* controls the expression of *Igf2r* gene by transcriptional interference with its promoter.[115] The other examples of lncRNAs involved in age-related gene methylation include *ecCEBP, pRNA, PAPAS, PTENpg1-AS* and *TARID*.

A healthy cell maintains a delicate balance of its protein content. This protein homeostasis is governed by protein biosynthesis, trafficking, and degradation. These processes influence different aspects of cell cycle, proliferation and senescence leading to aging. Various non-coding RNAs play important roles in these processes. Over-expression of lncRNA *HULC* decreases the expression of tumor suppressor p18 and inhibits apoptosis by autophagy and promotes cell proliferation and metastasis in gastric cancer cells.[116,117] The non-coding RNA *7SL* interacts with *TP53* mRNA and suppresses translation of p53. The RNA-binding protein Hur competitively displaces *7SL* to enhance p53 translation, thereby promoting cell cycle arrest and senescence.[118] *AS Uchl1*, an lncRNA with SINEB2 repeats, enhances the expression of ubiquitin carboxyl-terminal hydrolase-1 (UCHL1) inducing senescence.[119] The *lncRNA-p21* through translation repressors RCK and FMRP suppresses expression of β-catenin and JunB, which are involved in cell proliferation and carcinogenesis.[120]

During aging various environmental stresses, telomere dysfunction and DNA damage negatively influence the cell cycle progression leading to senescence. Senescence is induced by DNA damage in advancing age that elevates the expression of cell cycle inhibitors, e.g., p53 and p21. The lncRNAs involved in cell cycle regulation and senescence include *MALAT1, H19, ANRIL, SRA, HEIH, HULC, UCA1,* $NcRNA_{CCND1}$ and others.[27] Silencing *MALAT1* is associated with enhanced senescence and induced G1/S arrest indicating *MALAT1* as a senescence suppressor. The lncRNA *HEIH* down-regulates the expression of cyclin-dependent kinase inhibitors p16, p21, p27 and p57 assisting tumor cell growth.[121] Cell cycle regulator cyclin D1 (CCND1) associated lncRNA $NcRNA_{CCND1}$ is essential for the activity of cyclin-dependent kinases, cdk2 and cdk4 for G1/S transition. Upon exposure to DNA-damaging agents, $NcRNA_{CCND1}$ forms a nucleoprotein complex with protein TLS.[34] This complex interacts with CCND1 promoter to inhibit transcription. Thus, lncRNAs are associated with the different aspects of aging and are involved in almost every process in cell cycle, proliferation and senescence.

Conclusion

Extensive research in the field of non-coding RNAs and their roles in maintaining normal physiology as well as in disease pathogenesis suggest that lncRNAs are an important contributor to multiple disease traits. However, the answers of many ncRNAs mediated questions remain uncertain. Although many GWAS have linked them to different diseases, the actual mechanism of disease development is yet to be elucidated. The annotated databases of the lncRNA sequences in human genome are not complete or inaccurate in many cell types. Complete annotation of lncRNAs in specialized cells of different human organs is an important basis required for future work. The potential of lncRNAs as therapeutic targets and as biomarkers for different diseases warrants further investigation to explore their relevance in disease onset and progression. Therefore, we strongly expect that further studies of lncRNAs will reinforce the importance of these novel molecules in human biology and medicine.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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