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Environmental Health and Long Non-coding RNAs

Oskar Karlsson^{1,2,*} and Andrea A. Baccarelli²

¹Center for Molecular Medicine, Department of Clinical Neuroscience, Karolinska Institute, K8, 171 76 Stockholm, Sweden

²Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA

Abstract

An individual's risk of developing a common disease typically depends on an interaction of genetic and environmental factors. Epigenetic research is uncovering novel ways through which environmental factors such as diet, air pollution, and chemical exposure can affect our genes. DNA methylation and histone modifications are the most commonly studied epigenetic mechanisms. The role of long non-coding RNAs (lncRNAs) in epigenetic processes has been more recently highlighted. lncRNAs are defined as transcribed RNA molecules greater than 200 nucleotides in length with little or no protein-coding capability. While few functional lncRNAs have been well characterized to date, they have been demonstrated to control gene regulation at every level, including transcriptional gene silencing via regulation of the chromatin structure, and DNA methylation. This review aims to provide a general overview of lncRNA function with a focus on their role as key regulators of health and disease, and as biomarkers of environmental exposure.

Keywords

lncRNA; disease; chemicals; toxicology; epigenetics; smoking

Introduction

Several common diseases, such as cardiovascular disease, diabetes, and cancer, as well as neurodegenerative disorders, have genetic components, but are rarely caused by single genes or chromosomal abnormalities. Instead, a combination of genetic and environmental factors usually interact to influence an individual's risk of disease [1–5]. Epigenetics represents a promising research approach to understand this interaction. Epigenetic alterations modify the activation of certain genes, without directly affecting the DNA sequence. These modifications change in response to environmental stimuli, and can cause our cells to alter their gene expression. Epigenetic research is uncovering novel paths through which

*Corresponding author: Tel. +46 8 51776166; Oskar.Karlsson@ki.se.

Conflict of Interest

Oskar Karlsson and Andrea A. Baccarelli declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

environmental factors such as diet, air pollution, and chemical exposure can affect our genes [6–8]. DNA methylation and histone modifications are the most commonly studied epigenetic mechanisms. The role of non-coding RNA (ncRNAs), and especially long non-coding RNAs (lncRNAs), in epigenetic processes has been more recently highlighted.

lncRNAs are defined as transcribed RNA molecules greater than 200 nucleotides in length with little or no protein-coding capability [9]. As opposed to microRNAs (miRNAs) which are involved in transcriptional and post-transcriptional gene silencing via specific base pairing with their targets, lncRNAs regulate gene expression by diverse mechanisms that are not yet fully understood [9–12]. Although only a few functional lncRNAs have been well characterized they have been demonstrated to control gene regulation at every level including transcriptional gene silencing via DNA methylation and regulation of the chromatin structure [10, 13–16]. This review aims to provide a general overview of epigenetic control regulated by lncRNAs with a focus on their role as key regulators of health and disease, and as novel biomarkers of environmental exposure.

lncRNAs

The central dogma of molecular biology is centered on protein-coding genes, with DNA as carriers of the genetic information and RNA mediating information transfer from DNA to proteins that play important structural or functional roles essential for all aspects of life. This limited view of RNA function has been revised over the past decade with the discovery that animal genomes are subjected to pervasive transcription resulting in a variety of ncRNAs that play key roles in cellular functions beyond those previously attributed to RNA [17–20]. In fact, protein-coding genes represent only a small portion of the human genome (<2%), whereas the major part is transcribed into ncRNAs [18, 21]. ncRNA research has primarily focused on miRNAs, a small subclass of ncRNAs that regulate gene expression. More recently the attention has shifted to the larger, in both number and size, lncRNAs. More than 80% of the mammalian genome transcription is estimated to result in lncRNA generation, but molecular mechanisms and functional importance have been described only for a few [20, 22, 23]. lncRNAs, in contrast to many miRNAs, do not show strong evolutionary conservation and were originally classified as non-functional, transcriptional noise [24]. However, accumulating evidence has shown that lncRNAs are important players in diverse biological processes including: gene regulation, genome packing, chromatin organization, dosage compensation, and genomic imprinting [25–29]. They perform crucial roles in the control of gene expression during development and differentiation processes, and the number of lncRNA transcripts increases with the complexity of organisms—indicating the importance of lncRNA-based regulatory mechanisms in the evolution of multicellular organisms [30, 31].

Classification

lncRNAs are a heterogeneous class of RNAs, varying in nucleotide length (200 nucleotides to over 100 kilobases), cellular location (nucleus, cytoplasm, or both), and functional role in various biological processes. lncRNAs are often expressed at low levels and are generally more cell type-specific than the expression of protein-coding genes [30, 32, 33]. Similar to

mRNA, many lncRNAs are transcribed by RNA polymerase II (RNA pol II), capped, spliced, and polyadenylated [28, 34]. In addition, they can be transcribed from both sense and antisense strands of the genome [35]. LncRNAs can be classified by their genomic position relative to protein-coding genes and include the long intergenic ncRNA (lincRNA), intronic lncRNA, antisense lncRNA, transcribed pseudogene lncRNAs, and enhancer RNA [36].

Cellular functions

The intrinsic nucleic acid nature of lncRNAs gives them the dual ability to function as ligands for proteins and to mediate base-pairing interactions that guide lncRNA-containing complexes to specific RNA or DNA target sites, explaining their involvement in many regulatory functions [37–39]. Figure 1 shows examples of lncRNA cellular functions. In contrast to small ncRNAs, lncRNAs can fold into complex secondary and higher order structures, increasing the potential for both protein and target recognition [37–40]. LncRNAs can inhibit or facilitate the recruitment of RNA pol II, transcription factors and/or cofactors to gene promoters, thereby controlling transcription of target genes. They can also regulate alternative splicing of pre-mRNAs [41]. Moreover, their flexible scaffold nature enables lncRNAs to join multiple protein factors that would not interact or functionally cooperate if they relied solely on protein–protein interactions [37, 39, 42]. The scaffold function is also important for protein activity and localization as well as subcellular structures [43, 44]. Additionally, lncRNAs can guide specific chromatin remodeling complexes (e.g. Polycomb Repressive Complex 2; PRC2) to the correct chromosomal locations in cis or in trans providing target specificity to these complexes. Through these interactions lncRNAs can control local or global chromatin packing and the balance between transcriptionally active euchromatin and silent heterochromatin [28, 45]. Furthermore, lncRNAs can base-pair with mRNA molecules and affect their stability or translation as well as compete for miRNA binding and thereby preventing their function [46, 47]. Many lncRNAs may be processed into short ncRNAs such as siRNAs that can downregulate gene expression by degrading the mRNA transcripts [48–52]. Some lncRNAs may actually code for peptides and small proteins [53, 54].

lncRNAs, cancer and other disease

There is accumulating evidence that lncRNAs are important regulators of physiological and pathological responses [55–57]. Table 1 shows examples of lncRNAs that have been associated with human disease. The function of lncRNAs has mostly been studied in relation to tumorigenesis where they play important roles in the regulatory mechanisms of oxidative stress, inflammation, apoptosis, cell growth, and viability [23, 58–61]. For example, the HOX transcript antisense RNA (HOTAIR) plays a key role in gene regulation and chromatin dynamics and is misregulated in a variety of cancers [60, 62]. HOTAIR functions as a molecular scaffold that links the two histone modification complexes PRC2 and Lysine-specific histone demethylase 1 (LSD1) and modifies chromatin structure in trans to induce gene silencing and promote cancer cell proliferation, progression, and metastasis (Figure 1A) [60, 62]. HULC (highly upregulated in liver cancer) is another lncRNA that is associated with cancer. It can sequester and inhibit the function of several miRNAs,

including the tumor suppressor miR-372 (Figure 1E)[47, 63] However, dysregulation of lncRNA is not only associated with several types of cancers but a variety of human diseases including: cardiovascular disease [64–66], diabetes [67], membranous nephropathy [68], neural pathogenesis such as autism spectrum disorder and Alzheimer’s disease [57, 69, 70], and alterations of both the innate and adaptive immune system [71, 72]. Moreover, recent studies have revealed that lncRNAs also are localized within extracellular vesicles (EVs) and may be important for long distant intercellular communication and function as biomarkers [73–76].

Immune function

LncRNAs are emerging as important regulators of immune cell differentiation and activation [36, 77]. Several studies have reported aberrant expression of lncRNAs in various inflammatory conditions, including autoimmune and allergic disease [78–84]. For instance, a recent study discovered the novel C5T1lncRNA, in the rheumatoid arthritis risk locus TRAF1-C5, which influences transcript levels of C5 that are important for the pathogenesis [85]. Psoriasis is another autoimmune disorder generally thought to be a genetic disease triggered by environmental factors. PRINS (psoriasis susceptibility-related RNA gene induced by stress) is a lncRNA that may contribute to the psoriasis susceptibility [86, 87].

Metabolic disease

The regulation of metabolism and glucose homeostasis is a complex interplay of tissues/ organs and includes several mechanistically important lncRNAs [88]. For example, the lncRNA growth-arrest specific transcript 5 (GAS5) regulates cell growth and is induced under conditions of nutrient deprivation and cellular stress [89–91]. Functionally, GAS5 is both a precursor for small RNA [51] and a glucocorticoid receptor (GR) decoy (Figure 1B) [89]. By competing with GR DNA-binding sequences, GAS5 suppresses transactivation of GR-dependent gene promoters [89]. GAS5 also appears to repress the effects of other steroid hormone receptors [89] and may have a role in saving energy resources as an adaptive response to starvation by restricting the expression of steroid-responsive genes and has been reported to have proapoptotic functions [89–91]. Significant efforts have been made to reach a better understanding of the causes of diabetes at the molecular level [92]. Interestingly, Carter and coworkers have demonstrated that decreased serum levels of GAS5 were associated with type 2 diabetes in a cohort of U.S. military veterans [67].

Cardiovascular disease

Recent studies also suggest critical roles of lncRNAs in modulating the initiation and progression of cardiovascular disease [64, 93, 94]. LncRNAs such as Bvrt, Fendrr, ANRIL, MIAT, and MyHeart (Mhrt) play important roles in cardiovascular development and heart disease, including myocardial infarction, cardiomyopathy, heart failure, and atherosclerosis [66, 95–99]. For instance, Mhrt prevents myopathy in mice by binding to the helicase domain of Brg1, inhibiting chromatin targeting and aberrant gene regulation otherwise induced by this stress triggered chromatin-remodeling factor [95].

Brain disease

A significant part of all sequenced lncRNAs are expressed specifically in the brain, where they show strictly regulated temporal and spatial expression patterns [57, 100]. Genome-wide association studies and comparative transcriptomic studies have associated lncRNA expression with neurological disorders including schizophrenia, bipolar disorder, depression, autism spectrum disorder, Asperger's syndrome, attention deficit hyperactivity disorder, neuropathic pain, epilepsy, and neurodegenerative disorders such as amyotrophic lateral sclerosis, Alzheimer's and Parkinson's disease [57, 70, 101–103]. For example: the lncRNA BACE1-AS is transcribed antisense to the BACE1 gene and expressed at 2- to 6-fold higher levels in the brains of Alzheimer's disease patients compared to controls [69]. The BACE1 gene encodes a transmembrane beta-secretase protein that drives overproduction of pathogenic A β -42 peptides in Alzheimer's disease [69]. Functionally, BACE1-AS positively regulates BACE1 by binding to and stabilizing the BACE1 mRNA (Figure 1D). Experimental data suggest a positive feedback loop, in which BACE1-AS drives overproduction of toxic A β -42 peptides, which then further induce BACE1-AS overexpression and accelerating amyloid accumulation [69].

lncRNAs and environmental exposures

The role of miRNA in environmental health has been previously reviewed [6, 104–106]. Numerous studies demonstrate that miRNAs functionally interact with a variety of environmental factors including environmental chemicals, drugs, alcohol, cigarette smoking, viruses, and bacterial pathogens. It is therefore likely that lncRNAs are also important for driving exposure-disease associations or function as novel biomarkers of environmental exposure. However, while lncRNAs have been found to be dysregulated in a variety of human disease that are known to include environmental factors in the etiology, little is currently known about lncRNA interactions with environmental exposures. Most of the available data is derived from cell studies and no population-based studies have yet been published.

Cell studies

To adapt to environmental changes and survive different damages, eukaryotic cells have evolved networks of different protection mechanisms, including the heat shock response, which detect and controls diverse forms of stress. Heat shock proteins (HSPs) are produced by cells in response to exposure to environmental stressors, such as heat shock or various chemicals [107]. HSPs, also referred to as stress proteins, perform a chaperone function by stabilizing new proteins to ensure correct folding or by helping to refold proteins that were damaged by the stress [108]. The upregulation of HSPs is induced primarily by the heat shock transcription factor 1 (HSF1) and requires the lncRNA HSR1 [109, 110]. HSR1 undergoes a structural conformational change in response to heat shock, and forms a complex with the elongation factor eEF1A, stimulating the trimerization of HSF1, and thereby promoting activation of heat shock response genes [110]. More recently cell studies have shown that several lncRNAs respond to numerous environmental stressors such as genotoxic agents, ultraviolet (UV)-C irradiation, oxidative stress, cigarette smoke extracts, heavy metals, and endocrine disrupting chemicals [111–119]. For example, serum starvation

or exposure to translation inhibitors results in an increase in GAS5 that functions as a riborepressor for GR by binding to its DNA-binding domain leading to altered expression of several glucocorticoid-responsive genes. GAS5 has been reported to be proapoptotic and sensitize human cells to cell death by environmental stressors [111, 120]. Another example is PRINS, whose expression levels are increased by many stressors such as UV-B irradiation, viral infection, translational inhibition, and which may contribute to psoriasis susceptibility [86, 87].

Animal experiments

Increasing evidence suggests that lncRNAs take part in gene regulation, from the single gene to chromosome level, and cell studies have demonstrated that lncRNAs are involved in responses to external stimuli such as chemical exposure. However, to date, the *in vivo* effects of chemical toxicants on lncRNAs are not well studied. Martinez-Guitarte and coworkers analyzed lncRNAs levels after pollutant exposure of the aquatic reference organism *Chironomus riparius* [121]. Three lncRNA sequences were studied: telomeric repeats, Cla repetitive elements, and the SINE CTRT1, after 24-hour exposure to bisphenol A (BPA), benzyl butyl phthalate (BBP) and the heavy metal cadmium (Cd). BPA exposure upregulated both telomeric and Cla transcripts, whereas Cd and BBP did not significantly affect any of the sequences [121]. More recently, Bhan and coworkers investigated if the lncRNA HOTAIR, which is transcriptionally regulated by estradiol and a key player in breast cancer, is misregulated by BPA and diethylstilbestrol (DES) exposure [118]. The results revealed that HOTAIR expression is induced after exposure to nanomolar concentrations of BPA and DES in breast cancer cells (MCF7) as well as in the mammary glands of ovariectomized rats. Exposure to these endocrine disrupting chemicals leads to recruitment of estrogen-receptors (ERs) and ER-coregulators at the HOTAIR promoter, chromatin modification, resulting in an increased HOTAIR expression [118]. As HOTAIR is important for gene silencing and highly expressed in variety of cancers including breast tumors a chemically-induced increase in HOTAIR expression could potentially lead to adverse health effects [29, 42, 118].

Human exposure studies

Tobacco smoke is a complex chemical mixture containing thousands of compounds, several known to be carcinogens, cocarcinogens, and/or mutagens. Smoking is a common risk factor for the development of diseases such as cardiovascular disease, lung cancer, and chronic obstructive pulmonary disease (COPD). Genome-wide lncRNA expression in lung tissue resections from three non-smokers without COPD, five smokers without COPD and five smokers with COPD, showed that smoking alters the expression of lncRNAs [122]. Hundreds of differentially expressed lncRNAs (2-fold change) were found when comparing smokers and non-smokers with RNA44121|UCSC-2000-3182 and RNA43510|UCSC-1260-3754 being the most over- and under-expressed, respectively. Gene ontology and pathway analysis revealed that these lncRNAs are associated with changes in key pathogenic processes of COPD caused by smoking [122]. Although the number of subjects was low this study indicates that lncRNAs may play a role in the pathological changes generated by cigarette smoking. This is supported by cell studies reporting that cigarette smoke extracts increased levels of HOTAIR in human bronchial epithelial (HBE) cells.

HOTAIR then mediates epithelial-mesenchymal transition, a process involved in the malignant transformation of cells caused by cigarette smoke extracts [119]. Knockdown of HOTAIR by siRNA reversed the induced epithelial-mesenchymal transition, formation of cancer stem cells, and malignant transformation [119]. In addition, HOTAIR epigenetic silencing of p21 via enhancer of zeste homolog 2 (EZH2) mediated tri-methylation of Lys 27 of histone H3 contributes to changes in the cell cycle induced by cigarette smoke extracts [123]. Similar studies indicate that the lncRNAs MALAT1 also is involved in cigarette smoke extract induced epithelial-mesenchymal transition and malignant transformation of HBE cells [124].

Future perspectives

The developments in genomics and bioinformatics have resulted in a rapidly growing number of identified lncRNAs. Although an increasing number of lncRNAs are emerging as important disease players, surprisingly little is known about lncRNA's roles in environmental health. Studies are warranted to clarify whether and how lncRNAs may drive exposure-disease associations or function as novel biomarkers of environmental exposure. lncRNA interactions with a variety of environmental factors such as environmental chemicals, cigarette smoking and air pollution are likely. For instance, the health effects of ambient air pollution include allergic, respiratory, and cardiovascular diseases [125–127]. Numerous studies from the last several years have demonstrated that epigenetic modifications are susceptible to air pollution exposure and may be important for the biological mechanisms mediating these disease associations [128]. lncRNAs may be critical for the biological responses to air pollutants as they regulate numerous cellular processes suggested to drive these exposure-disease associations [129]. Furthermore, as lncRNAs have crucial roles in the control of developmental processes, they are also of particular interest in the context of the developmental origins of health and disease paradigm (DOHaD). Not only are population-based studies needed to establish lncRNA roles in environmental health, but experimental studies to clearly establish causality and detailed mechanisms are also warranted. However, as lncRNAs have a low evolutionary conservation integration of animal and human studies can be challenging.

Conclusion

Although only a small selection of all known lncRNAs have been functionally characterized to date, they have been demonstrated to control every layer of gene regulation including transcriptional gene silencing via regulation of the chromatin structure, and DNA methylation. Research shows that epigenetic and nonepigenetic mechanisms are involved in how the lncRNAs regulate various biological functions. Several lncRNAs have been reported to play an important role in the pathogenesis of human diseases, and their interactions with environmental exposure are exciting, but many questions remain unanswered. Further experimental and population-based epidemiological studies are warranted to clarify lncRNAs role in the interaction of genetic and environmental factors underpinning the development of many common diseases. Characterization of the specific roles of lncRNAs in epigenetic regulation and patterns of dysregulation in the lncRNAs-environmental factor

interactions can help to understand the mechanisms of diseases and provide insights into disease pathogenesis.

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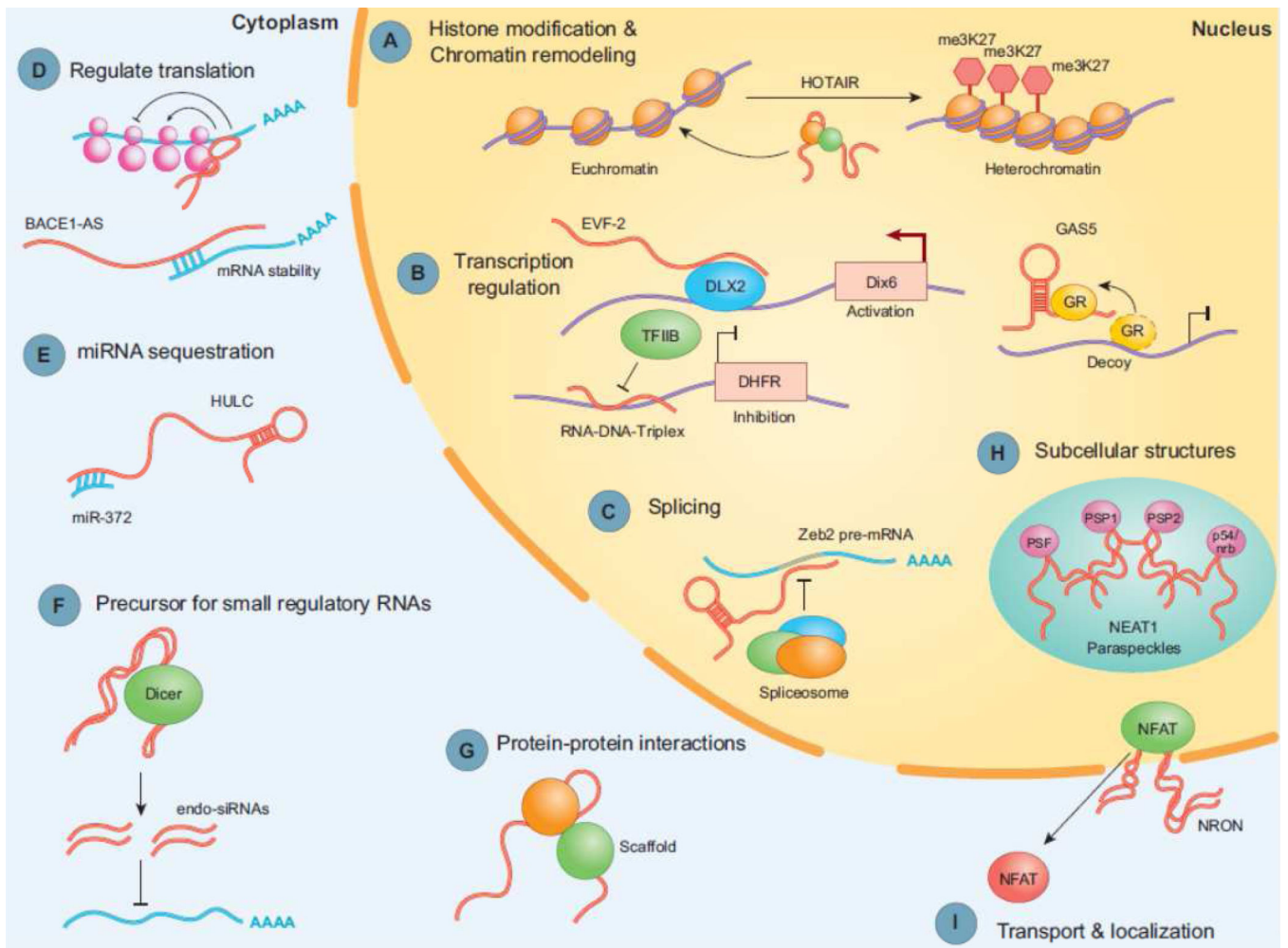


Figure 1.

Example of lncRNA cellular functions. lncRNAs can bind to DNA, RNA, and proteins and act in diverse ways within the cell. lncRNAs regulate gene expression by multiple mechanisms. They can guide chromatin remodeling complexes to the correct chromosomal locations controlling the balance between transcriptionally active euchromatin and silent heterochromatin both locally and globally (A). Furthermore, lncRNAs can inhibit or facilitate the recruitment of RNA pol II, transcription factors and/or cofactors to gene promoters, thereby controlling transcription of target genes (B). They can regulate alternative splicing of pre-mRNAs and thereby contribute to the transcriptome complexity (C). Moreover, they can affect the stability and translation of mRNA by base-pairing with mRNA molecules (D). lncRNAs can compete for miRNA binding and thereby preventing their function and influencing the expression of miRNA target gene expression (E). They can also be processed into small, single- or double-stranded RNAs that act as siRNAs and target other RNAs, which subsequently could result in target degradation (F). Their flexible scaffold nature enables lncRNAs to join multiple protein factors that would not interact or functionally cooperate if they only relied on protein-protein interactions (G). The scaffold function is also important for protein activity and localization as well as subcellular

structures (**H, I**). (Adapted from: Gutschner T, Diederichs S: The hallmarks of cancer: a long non-coding RNA point of view. *RNA Biol.* 2012 Jun;9(6):703–19) [59].

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Table 1

LncRNAs: Examples of biological functions and associations with human disease

Disease	lncRNA	Status ^I	Molecular mechanisms/role in disease	Ref.
Colorectal cancer (CRC)	PINT	↓	PINT acts as a tumor suppressor that reduces cell proliferation by regulating the expression of genes involved in p53 signaling via a PRC2-dependent mechanism.	[130]
Liver tumor	HULC	↑	HULC act as a molecular sponge that can bind and inhibit the function a number of miRNA, including the tumor suppressor miR-372.	[47, 63]
Breast, uterus, ovary tumors	SRA	↑	SRA forms ribonucleoprotein complexes with a number of nuclear receptors generally acting to stimulate transcriptional activation. SRA is a potential biomarker of steroid-dependent tumors	[131, 132]
Breast, colorectal tumors, prostate cancer etc	HOTAIR	↑	HOTAIR function as a molecular scaffold to link and target PRC2 and LSD1, leading to chromatin remodeling via H3K27 methylation and H3K4 demethylation and silencing genes implicated in inhibiting cancer progression/metastasis.	[29, 62, 133]
Breast tumor, type 2 diabetes	GAS5	↓	GAS5 act as a decoy and competes for binding to the DNA binding domain of the glucocorticoid receptor. GAS5 expression induces growth arrest and apoptosis. Decreased serum levels of GAS5 has been associated with diabetes	[67, 89, 91]
Cancer, type 2 diabetes, coronary artery disease, myocardial infarction	ANRIL	-	Several SNPs in the ANRIL locus on chromosome 9p are involved in coronary artery disease, diabetes and cancer. ANRIL binds PRC1/PRC2 and regulate the tumor suppressors CDKN2A/B. However, the clear role in the pathogenesis of these conditions is yet to be understood	[97, 134–138]
Myocardial infarction, diabetic retinopathy, schizophrenia	MIAT or GOMAFU	-	MIAT is involved in pathological angiogenesis and is suggested as a predictor of myocardial infarction. MIAT forms ribonucleoprotein complex with three splicing proteins, SRSF1, SF-1, and QKI. Downregulation of MIAT leads to alternative splicing, suggesting a lncRNA-driven mode of splicing-defect pathogenesis.	[57, 66, 139–141]
Alzheimer's disease	BACE1-AS	↑	BACE1-AS increases BACE1 mRNA stability leading to accelerated amyloid β42 accumulation	[69]
Autism spectrum disorder	MSNP1AS	↑	MSNP1AS regulates the moesin protein, regulator of synapse development and function, by stabilizing moesin mRNA. This mechanism may causally connect SNP variants in the MSNP1AS locus to autism spectrum disorder pathogenesis.	[70, 142]

^I ↓ downregulated, ↑ upregulated

LncRNAs are important regulators of physiological and pathological responses. Their role and functions have been mostly studied in tumorigenesis but dysregulation of lncRNAs is not only associated with several types of cancers but a variety of human diseases.

Abbreviations: PINT (p53-induced non-coding transcript), HULC (highly upregulated in liver cancer), SRA (steroid receptor RNA activator), HOTAIR (HOX transcript antisense RNA), GAS5 (growth arrest-specific 5), ANRIL (antisense non-coding RNA in the INK4 locus), MIAT (myocardial infarction associated transcript), GOMAFU (spotted pattern" in Japanese), BACE1 (beta-site APP-cleaving enzyme 1) BACE1-AS (BACE1 antisense RNA), MSNP1AS (moesin pseudogene 1 antisense RNA).