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Review Article

LncRNAs: The Ideal Composer of the Melody for Life

Qingyu Cheng[1], Shengwei Ke[1], A. R. Ghanam[1, 2], Xiaoyuan Song[1, *]

[1]CAS Key Laboratory of Brain Function and Disease, CAS Center for Excellence in Molecular Cell Science, School of Life Sciences, University of Science and Technology of China, Hefei, China

[2]Collage of Veterinary Medicine, Suez Canal University, Ismailia, Egypt

Email address:

songxy5@ustc.edu.cn (Xiaoyuan Song)

[*]Corresponding author

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Abstract: Long noncoding RNAs (lncNRAs), as major transcripts from the genome, are becoming indispensable keys to invisible doors linking to a new horizon, prompting a shift in the previous thoughts that lncRNAs are the transcriptional noises and by-products. The most puzzling fact, however, is that in spite of their pervasive regulation of many biological processes and diverse human diseases, their exact functions are still unclear. Here we review the regulations by lncRNAs at different levels, revealing some insights upon the molecular mechanisms and pathogenesis of related diseases.

Keywords: Long Noncoding RNA, Human Diseases, Epigenetic, Transcription, Post-Transcription

1. Getting to know lncRNAs: Identification and Classification

The central dogma of molecular biology suggests the flow of genetic information, from DNA to protein [1, 2], and proteins regulate most of life processes. However, the RNA world hypothesis considers RNAs to be responsible for all biological processes, which is supported by multiple lines of evidences, such as the existence of ribozymes that are capable of catalyzing specific biochemical reactions, similar to the actions of protein enzymes [3].

RNA molecules store information from DNA and transfer the processed useful messages to downstream proteins. Among these molecules, long noncoding RNAs (lncRNAs), as an intriguing class of non-protein coding transcripts no shorter than 200 nucleotides, are first described as a major component of the transcriptome in the large scale sequencing of full-length cDNA libraries in mouse [4].

During the past several years, thousands of lncRNAs have been identified and their functions in biological processes are still surrounded with aura of mystery [5, 6]. As the veil is gradually revealed, lncRNAs are coming into sights with several classifications containing enhancer RNAs (eRNAs)[7], promoter-associated RNAs (pRNAs)[8], natural antisense transcripts (NATs)[9, 10], intergenic lncRNAs (lincRNAs)[11, 12] and intronic lncRNAs [13] based on their genomic contexts (Fig. 1)[14]. Despite this "noncoding" concept, a group from New York University revealed that transcripts annotated as lncRNAs produce short peptides from small open reading frames (smORFs) that bind to, and inhibit, the sarco/endoplasmic reticulum calcium adenosine triphosphatase (SERCA), an ion pump essential for regulating calcium in the striated muscles [15].

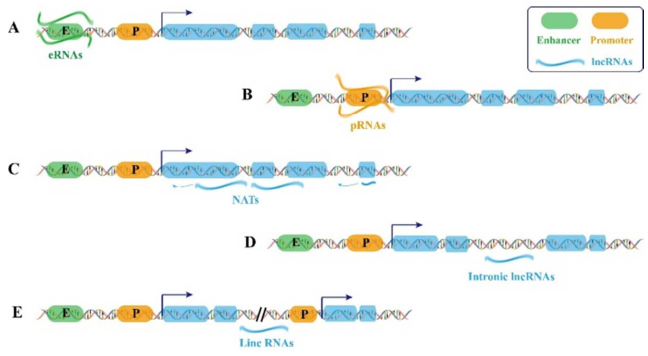

Figure 1. *Classifications of lncRNAs. (The figure is modified from Cao et al. [14]).*

2. lncRNAs Function and Human Diseases

With the innovations in next-generation sequencing technologies and computational biology, lncRNAs are gradually coming to the public's view from dark. They were once thought to be the noises and by-products of the pervasive transcription, without biological functions. However, an increasing number of reports elucidate lncRNAs participate in diverse biological processes and human diseases, especially cancers, like an ideal composer of melody for life, which arises expanding attention of researchers. By analogy to small non-coding RNAs that function mainly through base pairing to target transcripts, lncRNAs regulate the transcription and/or expression of target genes with their great structural plasticity, which is done by binding DNA, RNA, proteins or complexes in specific processes [16, 17]. The following are some of the recent regulatory models of lncRNAs at different levels in detail.

Epigenetic regulation

HOTAIR is a 2.2 kb lncRNA transcribed from the HOXC locus, and is required by polycomb repressive complex 2 (PRC2) for gene silencing of the HOXD locus in different chromosome [18]. The PRC2 mediates the dimethylation or trimethylation of histone H3 lysine 27 through its enzymatic subunits EZH1 and EZH2, responsible for gene silencing [19, 20].

In addition to that, as a modular scaffold, the HOTAIR 3' domain can bind to LSD1 complex, a lysine-specific demethylase, enabling their coordinate binding to target genes in chromatin [21].

Furthermore, overexpression of HOTAIR in epithelial cancer cells can induce genome-wide re-targeting of PRC2, leading to increased cancer invasiveness and metastasis, antagonistically, loss of HOTAIR can inhibit cancer invasiveness, particularly in cells that possess excessive PRC2 activity, indicating HOTAIR might be a critical target for clinical therapy [22].

Likewise, at epigenetic level, Air, lncRNA transcribed from an antisense promoter located in intron 2 of Igf2r, is required for the imprinted Slc22a3 and Igf2r genes silencing in mouse placenta [23]. In this specific interaction between Air and Slc22a3 promoter, Air accumulates at the promoter and recruits G9a, which results in methylation of targeted H3K9 and allelic silencing (Fig. 2A)[14, 23].

Transcriptional regulation

Dysregulated levels of HOTAIR were pervasively observed during cancer progression. Researchers demonstrate another HOTAIR-mediated gene regulation model that HOTAIR, through binding to Androgen-Receptor (AR), blocks the interaction between AR and E3 ubiquitin ligase MDM2, which prevents AR degradation and sequentially enhances AR transcriptional activity and potentiates prostate cancer cell growth and invasion (Fig. 2B)[24].

Besides this, high expression level and correlation with metastasis of HOTAIR are also prevalent in other cancer types, including colorectal [25], lung [26] and pancreatic cancers [27].

Another example for lncRNA functioning in transcriptional regulation is lncRNA*CCND1*, transcribed from the cyclin D (*CCND1*) gene promoter and inducible to a higher expression level by DNA damage signals. This lncRNA, as selective ligands, recruits RNA binding protein TLS to the *CCND1* promoter region and moderate the activities of the RBP, resulting in gene-specific repression (Fig. 2C)[28].

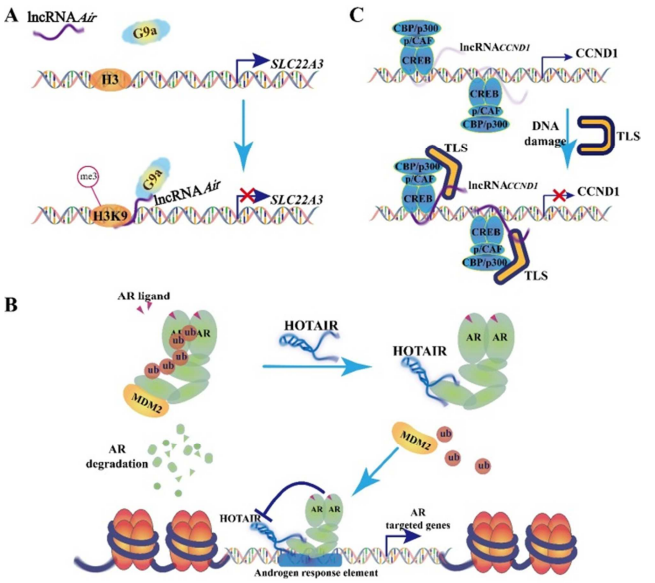

Figure 2. *A. lncRNA Air accumulates at the promoter and recruits G9a, which results in targeted H3K9 methylation and allelic silencing. (The figure is modified from Cao et al.[14]). B. lncRNA HOTAIR binds to Androgen-Receptor (AR) and blocks its interaction with E3 ubiquitin ligase MDM2, which prevents AR degradation and sequentially enhances AR transcriptional activity. (The figure is modified from Zhang et al[24]). C. lncRNACCND1 recruits RNA binding protein TLS to the CCND1 promoter region and moderate the activities of TLS, resulting in CCND1 gene repression. (The figure is modified from X. Wang et al.[28]).*

Post-transcriptional regulation

The natural antisense lncRNA BACE1-AS is a conserved RNA transcribed from the opposite strand of the BACE1 locus, with a 104 base pairs overlapping region of BACE1 [29]. While β-secretase 1 (BACE1) is involved in the sequential proteolytic cleavage of amyloid precursor protein (APP) to produce accumulative amyloid β-peptide (Aβ), which is an important indicator of Alzheimer's disease (AD)[30]. Experiments revealed that the expression level of BACE1 fluctuated as the same trend of BACE1-AS expressed. Further observations also confirmed the regulation of BACE1 expression by BACE1-AS at both mRNA and protein levels [29]. Additionally, the authors also proposed a model (Fig. 3) that cell stress promotes the increased expression of BACE1-AS, which sequentially increases expression levels of BACE1, as well as stability of BACE1 by forming RNA duplex. The elevated BACE1 proteins promote the APP processing and Aβ production. Toxic accumulative Aβ can further result in upregulation of BACE1-AS, facilitating the APP processing in a feed-forward manner [29].

BACE1-AS, as a conserved natural antisense lncRNA, regulates expression of BACE1 at mRNA and protein levels,

further regulating other processes, which sheds light on the clinical and medical therapy of AD.

Similar phenomenon comes together. Sirt1, also known as NAD-dependent deacetylase sirtuin-1, is a member of the sirtuin family of proteins [31], which play important roles in varieties of biological processes, containing cancer, adipose tissue, aging, cellular senescence and some other aspects [32]. Sirt1 AS is a natural antisense lncRNA transcribed from the opposite strand of Sirt1 with an overlapping region with Sirt1 mRNA [33]. And the regulatory model was clarified that Sirt1 AS could interact with Sirt1 mRNA by forming RNA duplex to promote Sirt1 translation by competing with miR-34a, inhibiting muscle formation [34].

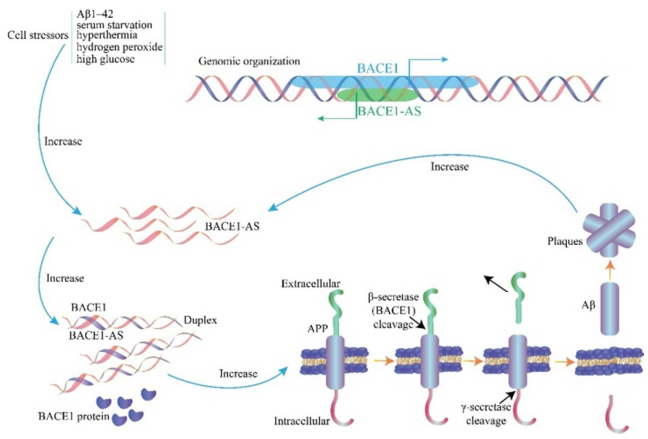

Figure 3. *Cell stressors increase the expression of BACE1-AS, resulting in increased expression levels of BACE1 and increased stability of BACE1 by forming RNA duplex. The elevated BACE1 proteins facilitate the APP processing and additional Aβ production, further resulting in upregulation of BACE1-AS.*

Metastasis associated lung adenocarcinoma transcript 1 (Malat1) is a large highly conserved lncRNA, which is abundant and primarily localized in nuclear speckles [35, 36]. Malat1 was discovered for the first time to have a higher propensity to metastasize in lung tumors [37], which is subsequently identified in multiple types of tumors [38, 39].

Genetic loss of Malat1 or knockdown with antisense oligonucleotides (ASOs) in the mouse mammary carcinoma model leads to slower tumor growth. Also, systemic knockdown with ASOs results in alterations in gene expression and numerous alternative splicing changes of protumorigenic signaling molecules and differentiation-related genes to make mammary tumors a less aggressive state [40]. Malat1 ASOs, as a promising therapeutic, provide a shining future avenue for primary human breast tumor patients. The researchers also proposed a model for the molecular mechanism, where Malat1 acts as a scaffold to coordinate transcription and pre-mRNA splicing in a gene- and context-specific manner (Fig. 4A)[40].

Post-translational regulation

A recently annotated lncRNA gene SAMMSON, which is consistently co-gained with MITF (a key regulator of melanoma progression but also serves as a central inhibitor of melanoma invasion [41]), expresses specifically in the vast majority of human melanomas. It promotes melanoma survival through interacting with p32, a master regulator of mitochondrial homeostasis and metabolism, to increase its mitochondrial targeting and pro-oncogenic function. Importantly, SAMMSON silencing decreases p32 protein level rapidly in mitochondria, accompanied by an increase in nuclear targeting (Fig. 4B). Further investigations are needed to figure out the potential role of SAMMSON as an informative biomarker in malignancy, and knocking down of SAMMSON disrupts vital mitochondrial functions in a cancer-cell-specific manner, which shows highly effective and tissue-restricted anti-melanoma therapy can be applied [42].

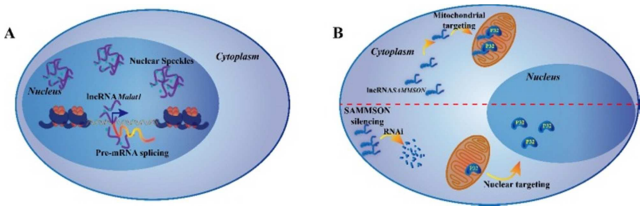

Figure 4. *A. Malat1 acts as a scaffold to coordinate transcription and pre-mRNA splicing of targeted genes. (The figure is modified from Arun et al.[40]). B. SAMMSON plays roles in melanomas through interacting with p32 to increase its mitochondrial localization and function, SAMMSON silencing rapidly decreases p32 protein level in mitochondria, and upregulates its expression in nucleus.*

Another long non-coding RNA named LincRNA-p21 was initially identified as a direct transcriptional target of p53 [43], it also acts as a suppressor of translation by directly associating with target mRNAs [44]. One study reported the functional role of lincRNA-p21 in the pathogenesis of atherosclerosis. Mechanistically, lincRNA-p21 directly binds to MDM2, leading to p53 release from MDM2, an E3 ubiquitin-protein ligase, and binding to p300, which thereby enhances p53 activity. While the expression of LincRNA-p21 dramatically decreases in coronary artery disease patients, and together with the result that lincRNA-p21 regulates cell proliferation and apoptosis during atherosclerosis, it is a potential therapeutic target to treat atherosclerosis and related cardiovascular disorders [45].

3. Concluding Remarks

As driven by emerging techniques and innovations, an increasing number of lncRNAs are pacing out of the shadows, thereby presenting new complexities to molecular mechanisms of human diseases, while providing new strategies for disease therapy as well. LncRNAs can function as several archetypes containing signals, decoys, guides and scaffolds [17]. Yet the vast majority of underlying mechanisms remain to be elucidated before we reach the nature of the lncRNA regulatory networks and their roles in various biological processes and human diseases. Indeed we have barely begun to scratch the surface of the lncRNA world. This is the exciting time for study of RNA biology.

Current bioinformatic tools or databases can offer researchers some guidance to reveal the relations between lncRNAs and diseases. MiTranscriptome, as a computationally

reconstructed portrayal of human transcription, is a catalog of human long RNA transcripts derived from computational analysis of high-throughput RNA sequencing (RNA-seq) data from over 6500 samples, indicating 7942 lineage- or cancer-associated lncRNA genes [5]. Another example is LncRNADisease, a database curated the experimentally supported lncRNA-disease association and also a platform that integrated tools for predicting novel lncRNA-disease associations [46]. Once we decipher the grammar rules of this noncoding language, we will be able to conquer the new continent, where dysregulated lncRNAs contribute to pathogenesis of diseases.

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References

[1] Crick, F. H., et al., *General nature of the genetic code for proteins.* Nature, 1961. 192: p. 1227-32.

[2] Yanofsky, C., *Establishing the triplet nature of the genetic code.* Cell, 2007. 128(5): p. 815-8.

[3] Fedor, M.J . and J. R. Williamson, *The catalytic diversity of RNAs.* Nat Rev Mol Cell Biol, 2005. 6(5): p. 399-412.

[4] Okazaki, Y., et al., *Analysis of the mouse transcriptome based on functional annotation of 60,770 full-length cDNAs.* Nature, 2002. 420(6915): p. 563-73.

[5] Iyer, M. K., et al., *The landscape of long noncoding RNAs in the human transcriptome.* Nat Genet, 2015. 47(3): p. 199-208.

[6] Rinn, J. L. and H. Y. Chang, *Genome regulation by long noncoding RNAs.* Annu Rev Biochem, 2012. 81: p. 145-66.

[7] Lam, M. T., et al., *Enhancer RNAs and regulated transcriptional programs.* Trends Biochem Sci, 2014. 39(4): p. 170-82.

[8] Marques, A. C., et al., *Chromatin signatures at transcriptional start sites separate two equally populated yet distinct classes of intergenic long noncoding RNAs.* Genome Biol, 2013. 14(11): p. R131.

[9] Katayama, S., et al., *Antisense transcription in the mammalian transcriptome.* Science, 2005. 309(5740): p. 1564-6.

[10] Faghihi, M. A. and C. Wahlestedt, *Regulatory roles of natural antisense transcripts.* Nat Rev Mol Cell Biol, 2009. 10(9): p. 637-43.

[11] Cabili, M. N., et al., *Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses.* Genes Dev, 2011. 25(18): p. 1915-27.

[12] Ulitsky, I. and D. P. Bartel, *lincRNAs: genomics, evolution, and mechanisms.* Cell, 2013. 154(1): p. 26-46.

[13] Guil, S., et al., *Intronic RNAs mediate EZH2 regulation of epigenetic targets.* Nat Struct Mol Biol, 2012. 19(7): p. 664-70.

[14] Cao, J., et al., *Three-dimensional regulation of transcription.* Protein Cell, 2015. 6(4): p. 241-53.

[15] Payre, F. and C. Desplan, *Small peptides control heart activity.* Science, 2016. 351(6270): p. 226-7.

[16] Wilusz, J. E., H. Sunwoo, and D. L. Spector, *Long noncoding RNAs: functional surprises from the RNA world.* Genes Dev, 2009. 23(13): p. 1494-504.

[17] Wang, K. C. and H. Y. Chang, *Molecular mechanisms of long noncoding RNAs.* Mol Cell, 2011. 43(6): p. 904-14.

[18] Rinn, J.L., et al., *Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs.* Cell, 2007. 129(7): p. 1311-23.

[19] Schaukowitch, K. and T. K. Kim, *Emerging epigenetic mechanisms of long non-coding RNAs.* Neuroscience, 2014. 264: p. 25-38.

[20] Margueron, R. and D. Reinberg, *The Polycomb complex PRC2 and its mark in life.* Nature, 2011. 469(7330): p. 343-9.

[21] Miao-Chih Tsai, O. M., Yue Wan, Nima Mosammaparast, Jordon K. Wang, Fei Lan, Yang Shi, Eran Segal, Howard Y. Chang, *Long Noncoding RNA as Modular Scaffold of Histone Modification Complexes.* Science, 2010.

[22] Gupta, R. A., et al., *Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis.* Nature, 2010. 464(7291): p. 1071-6.

[23] Nagano, T., et al., *The Air noncoding RNA epigenetically silences transcription by targeting G9a to chromatin.* Science, 2008. 322(5908): p. 1717-20.

[24] Zhang, A., et al., *LncRNA HOTAIR Enhances the Androgen-Receptor-Mediated Transcriptional Program and Drives Castration-Resistant Prostate Cancer.* Cell Rep, 2015. 13(1): p. 209-21.

[25] Kogo, R., et al., *Long noncoding RNA HOTAIR regulates polycomb-dependent chromatin modification and is associated with poor prognosis in colorectal cancers.* Cancer Res, 2011. 71(20): p. 6320-6.

[26] Nakagawa, T., et al., *Large noncoding RNA HOTAIR enhances aggressive biological behavior and is associated with short disease-free survival in human non-small cell lung cancer.* Biochem Biophys Res Commun, 2013. 436(2): p. 319-24.

[27] Kim, K., et al., *HOTAIR is a negative prognostic factor and exhibits pro-oncogenic activity in pancreatic cancer.* Oncogene, 2013. 32(13): p. 1616-25.

[28] Wang, X., et al., *Induced ncRNAs allosterically modify RNA-binding proteins in cis to inhibit transcription.* Nature, 2008. 454(7200): p. 126-30.

[29] Mohammad Ali Faghihi, F. M., Ahmad M Khalil, Douglas E Wood, Barbara G Sahagan, Todd E Morgan, Caleb E Finch, Georges St. Laurent III, Paul J Kenny & Claes Wahlestedt, *Expression of a noncoding RNA is elevated in Alzheimer's disease and drives rapid feed-forward regulation of β-secretase.* NATURE MEDICINE, 2008.

[30] Vassar, R., et al., *Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE.* Science, 1999. 286(5440): p. 735-41.

[31] North, B. J. and E. Verdin, *Sirtuins: Sir2-related NAD-dependent protein deacetylases.* Genome Biol, 2004. 5(5): p. 224.

[32] Rahman, S. and R. Islam, *Mammalian Sirt1: insights on its biological functions.* Cell Commun Signal, 2011. 9: p. 11.

[33] Wang, Y., et al., *Identification, stability and expression of Sirt1 antisense long non-coding RNA.* Gene, 2014. 539(1): p. 117-24.

[34] Wang, G.Q., et al., *Sirt1 AS lncRNA interacts with its mRNA to inhibit muscle formation by attenuating function of miR-34a.* Sci Rep, 2016. 6: p. 21865.

[35] Hutchinson, J. N., et al., *A screen for nuclear transcripts identifies two linked noncoding RNAs associated with SC35 splicing domains.* BMC Genomics, 2007. 8: p. 39.

[36] Bernard, D., et al., *A long nuclear-retained non-coding RNA regulates synaptogenesis by modulating gene expression.* EMBO J, 2010. 29(18): p. 3082-93.

[37] Ji, P., et al., *MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer.* Oncogene, 2003. 22(39): p. 8031-41.

[38] Yamada, K., et al., *Phenotypic characterization of endometrial stromal sarcoma of the uterus.* Cancer Sci, 2006. 97(2): p. 106-12.

[39] Lin, R., et al., *A large noncoding RNA is a marker for murine hepatocellular carcinomas and a spectrum of human carcinomas.* Oncogene, 2007. 26(6): p. 851-8.

[40] Arun, G., et al., *Differentiation of mammary tumors and reduction in metastasis upon Malat1 lncRNA loss.* Genes Dev, 2016. 30(1): p. 34-51.

[41] Golan, T., et al., *Interactions of Melanoma Cells with Distal Keratinocytes Trigger Metastasis via Notch Signaling Inhibition of MITF.* Mol Cell, 2015. 59(4): p. 664-76.

[42] Leucci, E., et al., *Melanoma addiction to the long non-coding RNA SAMMSON.* Nature, 2016. 531(7595): p. 518-22.

[43] Huarte, M., et al., *A large intergenic noncoding RNA induced by p53 mediates global gene repression in the p53 response.* Cell, 2010. 142(3): p. 409-19.

[44] Yoon, J.H., et al., *LincRNA-p21 suppresses target mRNA translation.* Mol Cell, 2012. 47(4): p. 648-55.

[45] Wu, G., et al., *LincRNA-p21 regulates neointima formation, vascular smooth muscle cell proliferation, apoptosis, and atherosclerosis by enhancing p53 activity.* Circulation, 2014. 130(17): p. 1452-65.

[46] Chen, G., et al., *LncRNADisease: a database for long-non-coding RNA-associated diseases.* Nucleic Acids Res, 2013. 41(Database issue): p. D983-6.