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Advances in Understanding Long Non-coding RNAs: Structural Variability and Implications in Cancer Biology

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Abstract: Long non-coding RNAs (LncRNAs), a subset of RNA molecules, were first identified approximately thirty years ago. These RNAs play essential regulatory roles in gene expression networks, influencing gene expression patterns through mechanisms such as chromosomal reorganization. Due to their diverse origins and the inherent versatility of RNA, LncRNAs exhibit a wide array of structures and properties. Extensive research has been conducted on the numerous LncRNAs in the context of cancer, uncovering their pivotal roles in the six key hallmarks of cancer: cell proliferation, cellular immortality, growth, metastasis, cell viability, and tumor angiogenesis. LncRNAs modulate these cancer hallmarks through various mechanisms, acting either as promoters or inhibitors. This review will examine the characteristics of LncRNAs and the mechanisms by which they influence the hallmarks of cancer.

Keywords: LncRNA, Cancer, gene expression, cancer hallmarks, genetic regulation.

1. Introduction

In recent years, due to the improvement of RNA sequencing technologies (RNA-seq), researchers are enabled to more effectively study the transcriptomes of organisms through large-scale RNA profiling. [1] The transcript screening in eukaryotic cells revealed the occurrence of multiple functional non-coding RNAs, varying in sizes and sequences, that are involved in various biological processes. [2] The discoveries of these RNAs explain the inconceivably large portion of the ncRNA, which is once recognized as genomic noises, occupies in eukaryotic transcriptomes, especially the transcriptome of mammalian cells. One category of the unveiled ncRNAs is LncRNA.

LncRNA consists of a broad variety of RNA species, most of which are non-coding RNAs (ncRNAs) that possess sizes greater than 200nt and cannot encode proteins, found in eukaryotes. [3] These molecules have structures resembling those of mRNAs since they undergo 7-methylation of guanine (m7G) of the 5' cap and polyadenylation (polyA) of the 3' tail (some of which do not possess) through transcription, which stabilize LncRNA molecules. LncRNA is subdivided into various classes based on their different biogenesis mechanisms, sizes, shapes, and functions. [4] Some [e.g. small nucleolus RNA-ended LncRNAs (snoRNAs) [5], enhancer RNAs (eRNAs) [6], promoter upstream transcripts (PROMPTs) [7], and intervening/ intergenic non-coding RNAs (lincRNAs)] are derived through ordinary RNA processing pathways, transcribed from areas such as exons, enhancers, promoter upstream regions, intergenic regions, while other classes of LncRNA (e.g. circRNAs), relatively rare, are generated through unique pathways [8-9].

2. Function of LncRNA

LncRNA engages in various crucial biological processes, both transcriptional and post-transcriptional, such as embryonic development and X chromosome inactivation. They function in manifold ways, which can be mainly divided into two types: chromatin-LncRNA interactions and RNA-LncRNA interactions; besides these common forms of interaction, LncRNA sometimes functions in unexpected ways. Through these interactions, LncRNAs are able to decoy proteins, serve as protein scaffolds, guide proteins (often genome modifiers) to their target sites, affect proteins allosterically, assist the function of enhancers, sponge miRNAs and mRNAs, and stabilize mRNAs.

2.1. Interactions with Chromatin

LncRNA-chromatin interactions have been broadly reported, and such interactions significantly affect the organisms' genetic regulation [10]. LncRNA functions commonly through two approaches with chromatin-in cis, by which LncRNA is tethered at where it is transcribed and functions nearby this transcription site, and in trans, by which LncRNA affects other chromosomal regions apart from the transcription site [11-12].

The X chromosome inactivation-associated LncRNA, XIST, involves in a typical in cis interaction by functioning at the site where it is transcribed. It interacts with a chromosomal architect, PRC2, and thus promotes X chromosome inactivation (Figure.1 A) by reconstructing the chromosome [13]. Additionally, in cis LncRNA interactions can promote the special rearrangement of the chromosome by recruiting genetic modifiers, altering the pattern of gene expression. For instance, the LncRNA HOTTIP (Figure.1 B) and Mira (Figure.1 C) recruit the histone H3K4-modifying complex MLL1 (HOTTIP also recruits WDR5), targeting this complex to the HOX gene locus, through which animal developments are rigorously regulated [14].

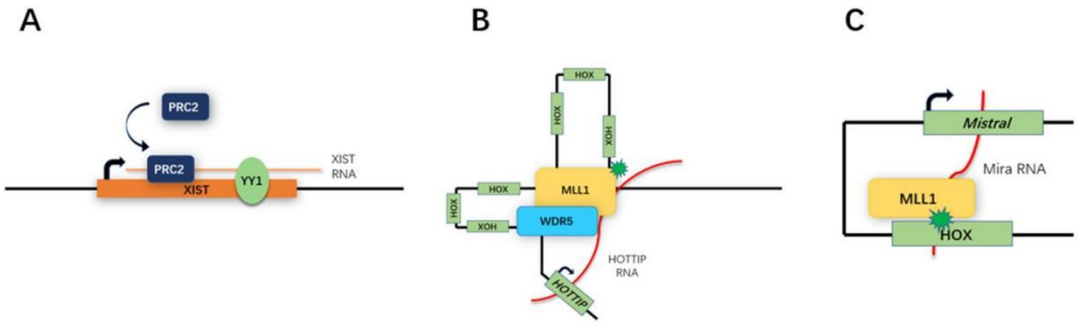


Figure.1 The in cis function of (A) lncRNA XIST, (B) HOTTIP, (C) and Mira. They all function at the site where they are transcribed.

Besides in *cis*, in *trans* LncRNA interactions are also both ubiquitous and important in the nucleus. The LncRNA HOTAIR serves as a scaffold of DNA-binding proteins and regulatory proteins (PRC2 and LSD1) at a gene locus other than its transcription site (Figure.2), regulating the gene silencing of this specific gene [15]. Also, LncRNA is enabled to function in *trans* through decoy—binding protein complexes and prevent them from binding to their proper regulatory targets. For example, methyltransferase DNMT1 inhibits the expression of a certain gene; when a particular LncRNA presents, it is decoyed away from its modification site and therefore allows the gene to express [16].

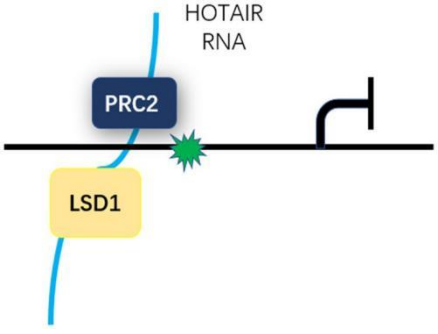


Figure.2 An example of in trans LncRNA-chromatin interaction: the HOTAIR RNA, which

serves as the scaffold of protein PRC2 and LSD1, regulating certain gene

2.2. Interactions with RNA

Apart from interacting with chromatin, LncRNA also affects a broad range of biological processes via interacting with other RNAs, such as miRNA, siRNA, and mRNA. In some cases, LncRNA renders mRNA to degrade, while under other circumstances, LncRNA stabilizes the mRNA. One such LncRNA interactions are involved in the pathogenesis of Alzheimer's disease (AD). As commonly known, the β-amyloid dimer is one of the most potent causes of AD, and β- secretase 1, whose transcript is named BACE1, promotes the accumulation of β-amyloid in neurons. The anti-sense transcript of BACE1, BASE1-AS, is a LncRNA that stabilizes the mRNA of BACE1 and thus regulates the expression of BACE1 (Figure.3 A). According to the research, BACE1-AS is up-regulated in AD, increasing the amount of BACE1 protein and, consequently, the production of β-amyloid [17].

Furthermore, the interaction between LncRNA and miRNA plays a significant role in the regulation of pluripotent cells. Three transcription factors-nanog, sox2, and oct4—are associated with the self-renewal and pluripotency maintenance of pluripotent cells, and the expression of these transcription factors can be inhibited by a miRNA: miR-145 (Figure.3 B). However, a LncRNA, linc-RoR, can sponge miR-145 due to its affinity to these miRNAs and subsequently release the inhibition imposed upon the expression of the three transcription factors; therefore, the cells can remain pluripotent [18].

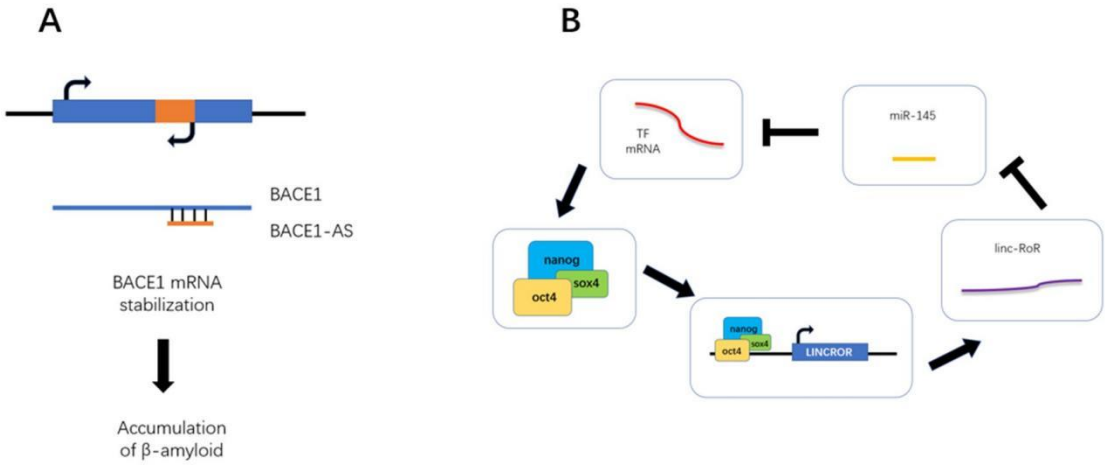


Figure.3 (A) The LncRNA BACE1-AS stabilizes BACE1 mRNA, promoting the accumulation of β-amyloid. (B) The interactions between transcription factors mRNA, linc-RoR, and miR-145, in which linc-RoR functions as a miRNA sponge.

2.3. Peculiar Cases

Though it is widely and consistently recognized that LncRNA does not possess capabilities to encode proteins, some researches proposed a striking and opposite result. Along with the development of technologies such as ribosome sequencing (Ribo-seq), Ribo taper, ORF-RATER, and PhyloCS, an increasing number of researches reveal that some specific LncRNAs and circRNAs are capable of encoding short peptides, usually possessing a size less than 100 amino acids. These short peptides can engage in various biological processes. Take HOXB-AS3 as an example. The LncRNA HOXB-AS3 [19] can be translated into a short peptide called HOXB-AS3 peptide which is able to compete with hnRNP A1 and regulate the alternative splicing of PKM1 (Figure.4 A); thus, the metabolism of the tumor can be controlled. Additionally, the short peptide SPAR (small regulatory polypeptide of amino acid response) encoded by the LncRNA linc00961 [20] is able to interact with v-ATPase in the lysosome and subsequently inhibits the activity of mTORC1 (Figure.4 B).

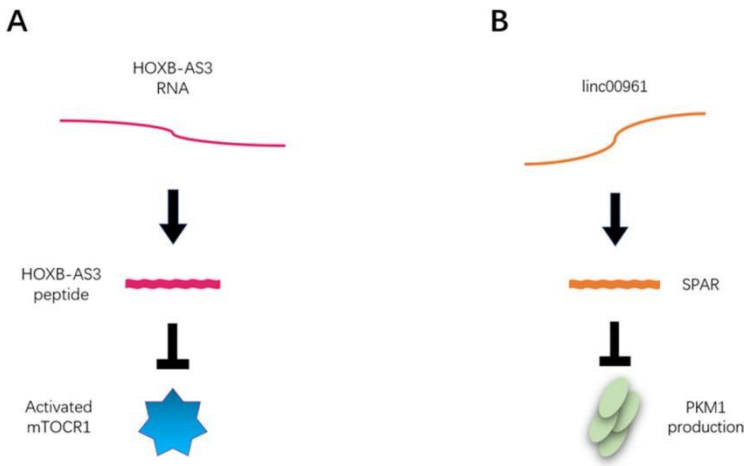


Figure.4 (A) HOXB-AS3 can be translated into a small peptide and inhibits the function of mTOCR1. (B) linc00961 codes a peptide called SPAR that inhibits PKM1 tetramer.

3. LncRNA and Cancer

Cancer is a series of genetic disorders that render the dysregulation and a cascade of cellular alteration, including the cells' abnormal growth and motility (or say metastasis). Since the dawn of medicine, researchers have been dedicated to unveiling the underlying mechanisms of the formation and malignancies of this significant disease. Currently, numerous molecular mechanisms of a tremendous amount of cancer have been elucidated, such as how mutations lead to carcinogenesis; these discoveries subsequently promoted the emergence of countless therapies, both target and broad-spectrum, which assisted human to withstand this daunting lesion.

Among the uncountable cancer-related processes, some are driven by a peculiar mechanism. Through genome-wide cancer mutation analysis, researchers revealed that a kind of molecule, apart from protein, also has extensive effects in the formation of cancer: long non-coding RNA. Due to the impressive versatility LncRNA manifests in the various cellular and molecular interactions, it plays exquisite roles in the genesis of diverse cancer phenotypes. LncRNA interacts with a series of biomacromolecules—proteins, DNAs, and RNAs themselves—which results in the derivation of multiple cancer phenotypes.

Until now, various LncRNA-associated cancer mechanisms were elucidated and reported [21], providing potential targets for the future development of therapies and references for the explanation of other cancers.

Though cancer is fundamentally regarded as a genetic disorder, it does not consist of a single type of genotype. Rather, it is composed of an aggregation of genotypes, resulting in dysfunctional intracellular regulation networks and intercellular communication that generate tumor microenvironment [22]. The modified and disrupted intracellular network in cancer cells results in the manifestation of six essential phenotypes [22-23] : self-sufficiency in growth signals, apoptosis evasion, insensitivity to anti-growth signals, tissue invasion and metastasis, limitless replicative potential, and sustained angiogenesis (Figure.5) ; these phenotypes collectively promote the malignancy of cancer and are recognized as significant traits of cancer. The role LncRNA plays in these hallmarks of cancer will be introduced in the following content.

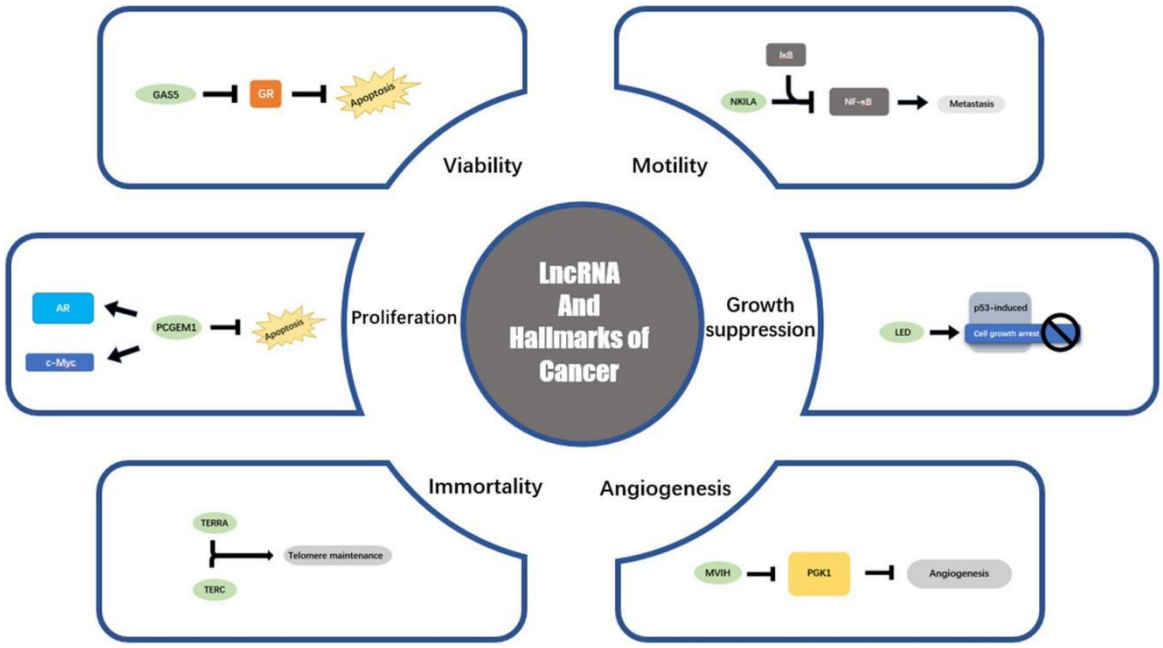


Figure. 5 An overview to the interactions of LncRNA rendering six cancer hallmarks.

3.1. LncRNA in Cancer Cell Proliferation

The proliferation of cells is often regulated by multiple hormonal pathways; in the LncRNA- related cancer cell proliferation mechanisms, it can be readily observed that hormonal pathways frequently serve as the target. The LncRNA prostate cancer gene expression marker 1, abbreviated as PCGEM1, is one of the most noticeable molecules that target hormonal pathways. PCGEM1 is highly associated with prostate cancer since it has been verified to present in more than 80% prostate cancer patients; additionally, this LncRNA is relatively overexpressed among African Americans, a group proven to have the highest prostate cancer incidence. When functioning, PCGEM1 activates androgen receptor (AR), which is demonstrated as a partial cause of prostate cancer cell proliferation. Also, PCGEM1 can increase cancer cell colony formation and confer resistance to doxorubicin-induced apoptosis through attenuating p53 and p21 responses. In research, the LNCaP cells, a prostate cancer cell line, had PCGEM1 gene knocked down, and an increase, in the long-term, of caspase 3 and 7 activity is observed in the cells, suggesting induced apoptosis. Meanwhile, the researchers overexpressed PCGEM1 in some cells, which resulted in the alteration of cell metabolic pattern to accommodate the cell growth; the expression of genes involved in glucose uptake, glycolysis, pentose phosphate pathway, and lipid synthesis was downregulated [24]. PCGEM1 is also shown to function as a c-Myc coactivator. Transcription factors such as c-Myc and HIF-1α are considered to be related to cancer cell metabolism. Using RNA immunoprecipitation, researchers found that PCGEM1 forms complex with c-Myc and assist it to function, while no similar relationship was found between PCGEM1 and other factors such as HIF-1α and p53. Using c-Myc-responsive luciferase construct, researchers also revealed that the overexpression of PCGEM1 is able to enhance the activity of c-Myc-inducing genes and promote cancer cell proliferation, even independent of the presence of androgen receptors [24].

3.2. LncRNA in Cancer Cell Viability

Cancer cells are able to survive mainly due to their selective advantage over other adjacent cells and multiple approaches to remain viable. The LncRNA called Growth arrest-specific 5, abbreviated as Gas5, is originally extracted from NIH 3T3 cell line, and following transcript sequencing revealed that Gas5 transcripts possess various alternative splicing patterns, resulting in different transcripts among which some are significantly involved in maintaining the viability in cancer cells [25]. The LncRNA Gas 5 functions by binding to the DNA binding site of, or decoy away, the glucocorticoid receptor (GR) and thus prevent the receptor from stimulating the glucocorticoid-responsive genes; the prevention of GR function downregulates the expression of cellular apoptosis inhibitor 2, therefore the apoptosis becomes more intense when the normal cells are under stressed conditions.

Gas5-related responses will be induced in some cancer cells, when they encounter nutrient deprivation or the absence of growth factor, data suggest that if the expression of Gas5 is diminished in breast cancer cells located adjoin to normal breast tissues, the viability is maintained in the breast cancer tissue under low nutrient environment. Some breast cancer cells also have a low Gas5 expression level without artificial intervention, supporting the correlation between Gas5 low expression and oncogenesis. Reversely, when Gas5 is overexpressed in the cells, the apoptosis is enhanced and the growth rate of the cells significantly decreases compared to the control [26].

Additionally, some transcripts of Gas5, such as U20, possessing small nucleolus RNA are also found to engage in the development of prostate cancer, indicating that these non-coding RNAs have unanticipated roles in the formation of clinically significant cancers [25].

3.3. LncRNA in Cancer Cell Growth Suppression

LncRNA is also involved in regulating tumor suppressors and cell growth arrest. An enhancer LncRNA called LED, identified through genome-wide enhancer RNA profiling, is suspected to have a potential tumor-suppressing function; as one of the evidence, LED is silenced in a p53 wild-type leukemia cell. It is demonstrated to interact and activates strong enhancers. Including CKDN1A, and thus promotes the p53-induced cell growth arrest. Since p53 functions by binding enhancers to regulate target genes, researchers screened p53-induced enhancers. However, the result revealed that while some enhancers contain p53 binding sites, the others do not. Therefore, the researchers assumed that the p53-induced LncRNA involves in the activation of enhancers by p53 since long non-coding RNA has been recognized as a crucial regulator. The research confirmed the hypothesis. The LED knockdown resulted in declined CKDN1A induction and activity and cell cycle arrest promoted by p53 [27].

3.4. LncRNA in Cancer Cell Motility

Cancer cells do not remain in one position when developing in the human body, rather, they metastasize to different organs and form new colonies. Various LncRNA has been identified as essential regulators of cancer cell metastases and motility. One LncRNA called MALAT1, a highly conserved LncRNA was found to be strongly correlated with the high risk of metastasis in early-stage non-small cell lung cancer [28]. Research has shown that adenocarcinoma and squamous cell carcinoma patients with low MALAT1 expression levels had a higher survival during a 5- year follow-up period. In addition, it was discovered that though MALAT1 has no clear function in the normal tissue, verified by examining MALAT1 loss-of-function mice, knocking down MALAT1 in lung carcinoma cells significantly marred the in vitro motility of cells, indicating that even this LncRNA's function is ambiguous in normal tissues, MALAT1 overexpression possibly confers cancer tissues important phenotypes [29].

Another LncRNA provided us a new angle of the connection between the tumor microenvironment and the LncRNA regulation of cancer metastasis. The LncRNA NKILA disrupts the NF-kB signaling pathway by binding to NF-kB/IkB complex, masks the phosphorylation site of IkB, and therefore suppresses metastasis. The suppression of NKILA often renders poor prognosis of breast cancer patients [30]. Yet, NKILA is not induced by intracellular factors, instead, it is induced by NF-kB as the response of inflammatory signaling, suggesting that intercellular environments can impact LncRNA-related metastasis.

3.5. LncRNA in Cancer Cell Immortality

Different from normal cells, cancer cells possess the ability to maintain their immortality through unique mechanisms of telomere maintenance. In normal cells, telomeres senesce after each replication, and the truncation of telomere eventually renders cells' mortality. In many human tumors, the overexpression of reverse transcriptase TERT, which maintains telomere, is observed; also, research also revealed that single nucleotide polymorphisms in the telomere RNA component, abbreviated as TERC, gene are associated with telomere lengthening and can possibly lead to invasive cancer [31]. Telomeric repeat containing RNA (TERRA), transcribed from telomeric DNA, also plays crucial roles in telomere maintenance. For instance, TERRA modulates the exchange of single strand DNA binding protein RPA by POT-1 and therefore regulates telomere

capping. [32].

3.6. LncRNA in Tumor Angiogenesis

Same as normal tissue, tumor tissues need a blood supply to survive and develop, especially for rapidly growing tumors. In order to gain blood supply, tumor cells can release angiogenic factors (e.g. fibroblast growth factor and vascular endothelial growth factor families) to induce angiogenesis and promote blood vessel to grow in the tumor. Additionally, angiogenesis in the tumor helps cancer cells to enter the bloodstream and spread to other organs and parts of the body. Thus, angiogenesis is essential for cancer development and metastasis.

A LncRNA named MVIH has been discovered as the inhibitor of PGK1, which inhibits angiogenesis, and can thus disengage the inhibition imposed upon angiogenesis. This LncRNA is located at the intron of the ribosomal protein S24 gene (RPS24), while no correlation is shown between the expression level of RPS24 and MVIH. The investigation about the clinicopathological features of MVIH revealed that in the patients possessing higher MVIH expression level and low RFS ($P<0.001$) and survival after hepatectomy, indicating the correlation between high MVIH expression and poor prognosis [33]. In addition, the research showed that the PGK1 concentration in the MVIH-overexpressing cells is significantly lower than that of the control; to further verify the MVIH's impact in angiogenesis induction, researchers employed in vitro capillary tube formation assay found that human umbilical vein endothelial cells developed more capillary-tube-like structures with the TCM from cancer cells transfected with MVIH compared to those developed in the control cells.

4. Future Perspectives of Lncrna Research

Researchers have contributed enormously to the identification, characterization, and elucidation of LncRNA and their mechanism of function and have established a generally comprehensive framework of interactome between LncRNA and other biomacromolecules. The efforts made are incontestably valuable and significant for our journey to unveil the fundamental mechanisms of cells, yet it can also be perceived that the current studies are partially incomplete and somewhat unstandardized and require to be further integrated with other fields.

It is conspicuous that a large portion of the current studies merely revealed the relationships and correlations of LncRNAs and biological processes, while the underlying molecular mechanisms, including exhaustive LncRNA sequences and structures, interacting loci, and triggered cellular pathways, of these correlations, were not sufficiently accounted for. However, due to the improvement of RNA sequencing (RNA-seq) technology and derived sequencing technologies, such as ribo-seq, the development of new research techniques, like chromosome isolation by RNA purification sequencing (ChiRP-seq), and the coupled use with other techniques such as mass spectrometry, researchers are more enabled to discover the elaborate mechanisms previously unable to be reached. Equipped with more advanced technologies and methodologies, future researchers ought to progressively alter their focus to the elucidation of the essential mechanisms of previously reported correlations; only with the discovery of these molecular mechanisms we can develop more target therapeutics and fight cancer. Some approaches leveraging molecular knowledge of LncRNA have been implemented: specific RNA interference has been employed to deplete certain cytoplasmic LncRNA, and anti-sense oligonucleotides have designed to complement with some particular LncRNA and direct RNase H to degrade them [34]. These methods gained great success in treating solid tumors and lymphoma [35].

Apart from the molecule-scale exploration, the need for standardizing LncRNA-related research is also imperative. LncRNA plays a major role in numerous biological processes and can be frequently detected as a marker responsive to some specific cellular processes, such as metastasis, as described in multiple research. This process-specific feature has been long noticed and regarded as a breakthrough in disease diagnosis, including cancers and developmental disorders. Also, LncRNAs are considered as potential targets for novel therapies. Yet, it has to be acknowledged that a tremendous number of LncRNAs have not been identified; for those identified and characterized, few can be applied clinically. The standardized research procedures, such as protocols of

identification of LncRNA, the stability of LncRNA in body fluid, sample preparation, and development of detection and delivery vector, in different tissues and under different circumstances is urgent to be developed.

Being standardized, LncRNA can be more ideally analyzed and used in multiple situations and even be utilized accompanying other fields' knowledge, such as physics and informatics. Particularly, LncRNA has great potential in being used in synthetic biology. The characterized LncRNA can be introduced into complex engineered biological systems to serve as regulatory components, such as in engineered yeast. Further, being equipped with more accurate mathematical models, researchers will be able to design, de novo, LncRNA that can specifically bind to a certain substance, block the interacting site of a protein, and sponge some particular miRNAs through complementary pairing; thus, they can be more efficiently used in synthetic biosystems. Moreover, it has been discovered that LncRNAs can self-assemble with other RNAs and proteins and form a phase-separating structure called microbody. The microbodies, being further designed, can serve as phase-separating organelles or genetic regulatory components.

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