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Review: Biological Bases and Characterization of Long Non-Coding RNAs

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A B S T R A C T

Long non-coding RNAs (lncRNAs) were known not so long ago as a type of diverse non-coding RNAs that have received much attention due to their multiple regulatory activities at the nuclear and cellular level and their essential participation in the regulation of many chemical and biological activities. Although lncRNAs are expressed at low levels, they do not encode proteins, are insufficiently conserved, and act by various mechanisms. However, some characteristics and functions of several copies of lncRNAs separate them from other forms of non-coding RNA have been discovered. Here we will look at how events develop in lncRNAs and talk about their main biological properties and influences, as well as how to achieve such a wide range of functions using a variety of mechanisms such as protein transfer, gene transcription, chromatin rearrangement, unique properties, and other biological activities.

Abbreviations:

ANCR Anti-differentiation noncoding RNAs
ANRIL Antisense noncoding RNAs in INK4 locus
asRNAs Antisense lncRNAs
BACE1-AS Beta-site amyloid precursor protein cleaving enzyme 1 antisense lncRNAs
CARL Cardiac apoptosis-related lncRNAs
cirNAs Circulating nucleic acids
cis-NATs Cis-natural antisense transcripts
HOTAIR Hox transcript antisense intergenic RNAs
lincRNAs Long intergenic non-coding RNAs
lncDCs Long noncoding RNAs dendritic cells
lncRNAs Long non-coding RNAs
LSD1 Lysine-specific demethylase-1
MALAT1 Metastasis-associated lung adenocarcinoma transcript 1
miRNAs Micro RNAs
mRNAs Messenger RNAs
NATs Natural antisense transcripts
Pol II Polymerase-II
Poly-A Polyadenylated
PRC2 Polycomb repressive complexes-2
SENCR Smooth muscle and endothelial cell-enriched migration/differentiation-associated lncRNAs
STAT3 Signal transducer and activator of transcription 3
THRIL TNF-α and heterogeneous nuclear ribonucleoprotein L-related immunoregulatory lincRNAs
TIN Totally intronic noncoding
TNF-α Tumor necrosis factor-alpha
Trans-NATs Trans-natural antisense transcripts
ZEB1 Zinc finger E-box-binding homeobox 1

1. INTRODUCTION

Long non-coding RNAs (lncRNAs) are a diverse group of transcripts participatory in a wide range of biological and chemical activities in all aspects of organisms and biosynthesis [1]. Although lncRNAs were first described as similar transcripts for the messenger RNAs (mRNAs), which do not code a protein, a fresh flurry of experimental investigation had already shown the distinct characteristics

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that set them apart from encoding transcripts [2]. However, can clarify the simple definition of lncRNAs as copies longer than 200 nucleotides (nt), some of which lack coding the proteins. Based on their length, they have been distinguished from other types such as small which are less than 100 (nt) and the medium which are less than 200 (nt), which differ not only in length but there are structural, functional, and organizational differences between them [3].

Among the subordinate type of non-coding RNAs, lncRNAs are the most numerous, outnumbering RNAs protein-coding. lncRNAs have also been identified as important regulators in various chemical and biological activities, including genetic organizing and cellular apoptotic, propagation, rotation, metabolites, distinction, and others [4]. There are some characteristics common to most lncRNAs and mRNAs, as they are transcribed by the same enzyme, which is RNAs polymerase-II (Pol II), as well as they have the same number of polyadenylated (poly-A), copies and spliced, while they differ from mRNAs, and can be distinguished through some characteristics such as there have low levels of expression, they are smaller in size compared to mRNAs, in addition to containing lengthy and little exons [5].

lncRNAs can be found in a wide range of organisms, both unicellular and multicellular. Sometimes the secondary organization of lncRNAs is preserved across kinds while poorly preserved in sequence and progression [6]. lncRNAs can be found in the cytoplasm as well as in the nucleus and are categorized according to the transcriptional trend and position to carry out their biological and pathological roles. They are also transferred to many cellular sites within cells to perform a variety of controlled roles and several chemicals and biological actions [7].

To carry out their tasks in the cytoplasm and nucleus, the cytoplasm lncRNAs are thought to act by engaging with working as modulation components and proteins for RNAs-connecting in the cytoplasm, while the nucleus lncRNAs play a variety of tasks via chromatin adjusting, copy control, and serving as a component of the nucleus buildings [8]. In general, much research has focused on the genetic potential of lncRNAs as well as the limited capabilities of coding proteins due to the lack of global reading frames. Therefore, this review will outline the literature of evidence for the biological levels and important characteristics correlated with taxonomic, locational, and functional mechanisms of lncRNAs.

2. CLASSIFICATION OF LONG NON-CODING RNAS

lncRNAs can be grouped into various categories based on genomic localization, structure, and function [9]. In general, lncRNAs can be divided into intergenic or intragenic according to their positions in the genome or action with protein-coding genes [10]. However, long intergenic non-coding RNAs (lincRNAs) do not interfere with protein-coding genes, while the intragenic can interfere with protein-coding genes. They are categorized into four subclasses includes antisense, bidirectional, intronic, and sense lncRNAs [11].

Antisense lncRNAs (asRNAs) are transcriptase from the opposite strand of a protein-coding gene and may be divided into natural antisense transcripts (NATs) includes trans-NATs which organizes the expression of genes at other sites, especially unpaired genes, and cis-NATs that usually serves to organize the expression of the matching sense transcripts [12]. Bidirectional lncRNAs are located adjacent to the coding genes on the counteractive strand of the protein-coding genes and have promoters transcribed in the opposite trend [13]. Intronic lncRNAs reside within protein-coding genes and do not interfere with encoded exons and may contain some transcripts that arose from RNAs processing or on independent transcripts such as intronic circulating nucleic acids (cirNAs), or on independent transcripts as totally intronic noncoding (TIN). Sense lncRNAs can interfere with multiple exons of a different or adjacent gene and transcribe in the same trend of the gene [14].

3. MECHANISMS AND FUNCTIONS OF LONG NON-CODING RNAS

Long non-coding RNAs (lncRNAs) can express multiple genetic processes due to their regulatory, structural, functional, and interacting properties with many cellular, protein, and nucleic acid molecules and participating in these interactions and processes at low levels [15]. However, the signals, decoys, guides, and scaffolds are all examples of techniques that lncRNAs can use to perform the job of gene modulation [16, 17]. Signal lncRNAs play a role in molecular messaging by being transcribed at specific space-time locations to read the intracellular milieu or react to specific triggers [18]. Decoy lncRNAs may behave as molecular harpoons, attracting RNA-binding proteins like transcriptional regulators and histone modifications enzymes, and other RNA sequences like micro RNAs (miRNAs), to influence cellular physiological systems [19].

By building aggregates with ribonucleoproteins and guiding their distribution to specified chromatin sites, guidance lncRNAs are frequently used as molecular aides. By constructing compounds with this kind of chemical composition that operates as transcriptional activation, scaffold lncRNAs might act as key substrates for the transcription [3, 20]. lncRNAs possess multiple mechanisms during translation and transcription of genes that are responsible for regulation and gene interaction with proteins by serving as scaffolding, recruiting chromatin-modifying complexes [21], and activating or stabilizing proteins at specific genetic sites to achieve optimal regulation and gene

expression [22]. Cis-natural antisense transcripts (cis-NATs) can express and affect chromatin structure via regulating transcription processes and induct regulatory complexes to proximal genomic sites in addition to their ability to regulate genes in a manner independent of lncRNAs [23].

lncRNAs can work with genetic processes through the manipulation and rotation of RNA and is responsible for the degradation or translation of messenger RNAs as well as its work with epigenetic processes in the regulation of many transcripts and chromatin remodeling [24]. Subcellular localization is important for the mechanisms of action of lncRNAs because these molecules can be located in different locations such as cytoplasm and chromatin, in addition to their presence in the nuclei, based on the structural design [25]. For example, lncRNAs metastasis-associated lung adenocarcinoma transcript 1 (lncRNAs MALAT1) can interact with splicing factors and affect their allotment in nuclear stains by acting as a molecular sponge [26].

Table 1 demonstrates a group of lncRNAs related to many biological activities and functions. However, anti-differentiation noncoding RNA (ANCR) inhibits the differentiation pathway to preserve epidermal adult bone marrow cells [27]. Moreover, cardiac apoptosis-related lncRNAs (CARL) work as microRNA-539 genes in cardiac muscle cells and inhibit them from apoptosis and cleavage [28]. Tumor necrosis factor-α and heterogeneous nuclear ribonucleoprotein L-related immunoregulatory lincRNAs (THRIL) are regulatory expresses of cytokines such as TNF-α and inflammatory response [29].

lncRNAs can form a double or triple hybrid structure of RNA-DNA, the fetal lethal noncoding developmental regulatory (lncRNAs Fendrr) act to compose the tertiary structure in the district of gene promoters [30], as well as act to regulate remote and proximal genes by recruiting polycomb repressive complexes-2 (PRC2) on some target genes and sequences in mammalian [31]. lncRNAs hox transcript antisense intergenic RNAs (HOTAIR) act to inhibit specific genes by recruiting PRC2 and lysine-specific demethylase-1(LSD1) by forming a triple structure with AG-rich patterns in the specific gene promoters area of the medical signaling cells [32]. Antisense noncoding RNAs in INK4 locus (ANRIL) participatory in inflammations and arteriosclerosis and related with the disorder of vascular endothelial cells and associated with the growth and apoptosis of cardiac muscle cells [33]. Smooth muscle and endothelial cell-enriched migration/differentiation-associated lncRNAs (SENCR) have the ability to regulate the endothelial cells in the angiogenesis of the cells separated from the veins of the umbilical [34]. Long intergenic noncoding RNA predicting cardiac remodeling (LIPCAR) is a predictor for cardiovascular diseases and is related to clinical acuteness [35]. Long noncoding RNA dendritic cells (lncDCs) are linked to signal transducer and activator of transcription 3 (STAT3) and activated to regulate the differentiation of dendritic cells [36].

Natural antisense transcripts (NATs) can regulate alternative splicing of genes by forming the duplex structure with pre-mRNA [37]. In epithelium cells, the RNA-RNA double structure is formed by binding lncRNAs NATs with zinc finger E-box-binding homeobox 1 (ZEB1) gene to stop the binding of the large ribonucleoprotein complex and translate the Zeb2 gene [38]. Beta-site amyloid precursor protein cleaving enzyme 1 antisense lncRNA (BACE1-AS) are lncRNAs from the antisense string of β-endocrine enzyme-1 gene that can create a double structure with BACE1 mRNAs, which leads to improved mRNA synthesis and can be induced stability or higher regulation of BACE1 protein levels [39]. However, BACE1-AS regulates neuronal functions, and it could be a possible biomarker in Alzheimer's disease [40].

Table 1: Some types of lncRNAs and their biological activity in the different body actions.

Type of lncRNA	Function	References
lncRNAs-ANCR	Inhibits differentiation pathway to preserve epidermal adult bone marrow cell.	[27]
lncRNAs-CARL	Inhibits cardiac muscle cells from apoptosis and cleavage.	[28]
lncRNAs-ANRIL	Involved in arteriosclerosis related to the disorder of vascular endothelial cells as well as to growth and apoptosis of cardiac muscle cells.	[33]
lncRNAs-SENCR	Regulate the endothelial cells in the angiogenesis of the cells isolated from the veins of the umbilical.	[34]
lncRNAs-LIPCAR	Predictor for heart diseases and related with the clinical severity.	[35]
lncRNAs-DCs	Binds to signal transducer and activator of transcription 3 (STAT3) and activated for regulating the differentiation of dendritic cells.	[36]
lncRNAs-THRIL	Regulatory expression of inflammatory response and cytokines such as TNF-α.	[29]
lncRNAs-BACE1-AS	Regulations neuronal functions and It could be a possible biomarker in Alzheimer's disease.	[40]

4. CHARACTERIZATION OF LONG NON-CODING RNAS

lncRNAs are a type of non-coding RNAs (ncRNAs) that predominantly found in the nucleus and make up a significant portion of the genome with tallness much over 200 (nt) [2], many conformational aspects of lncRNAs are discovered to be similar to those that have fewer transcriptions, are commonly have a five-prime cap, splicing,

and three ends (poly-A) [41]. lncRNAs are preserved by cell kind and can change in reaction to external or during evolution. The secondary construction of lncRNAs appears to be preserved amongst strains, whilst their sequence is infrequently preserved [42].

According to several data, the genetic information is expressed into RNA about 85 percent, but approximately 2 percent of total gets translated to proteins. lncRNAs are one of these non-coding genes that are being linked to a growing variety of biochemical and pathological pathways [43]. lncRNAs are required for cell proliferation and evolution, progression of cancer, as well as different purposes, during numerous non-genetic influences on the gene expression, lncRNAs either suppresses or stimulate transcriptional activation [44].

lncRNAs are a unique type of genes that are discovered to be frequently transcribed in the genes, polymorphisms, mutation, and illnesses that cause a wide range of pathologies [45]. The long size of lncRNAs enables them to coil into a more useful form and be given something like a physiological role, despite their inability to encode proteins [22]. lncRNAs induce the expression by reacting with DNAs, RNAs, and proteins, yet it is linked to human disorders through various techniques, including changes in the expression, apoptotic, and cell signaling [46]. lncRNAs are greater than two Kb long, with a coding possibility of smaller than one hundred amino acids. Protein-coding genes likely account for twenty percent of transcription activity in the genetic code, and these data demonstrate that lncRNAs sequences are much greater than encoding sequence information for RNAs [9].

For characteristic modification for genetic expression and protein composition, various groups of lncRNAs have different ways of acting; cell-special development is found in lncRNAs, so each is shown to be transcribed at a given moment, and they can act as molecular indicators in response to a wide range of triggers [47]. Furthermore, lncRNAs could be discovered in a variety of organs, reflecting their vast range of biological characters, while the brain tissue and central nervous system show to get the largest selection of generated lncRNAs [48]. In addition, lncRNAs could be located in a variety of cellular organelles, such as the nucleus and the cytoplasm, where they appear to be most abundant [49].

5. BIOGENESIS OF LONG NON-CODING RNAS

The biogenesis of lncRNAs is generally dependent on the same approach as the transcription process for protein-coding and necessitates the assistance of the traditional factors of RNA polymerases like pre-initiation, elongation, and particular factors [41]. The biogenesis of lncRNAs molecules is often like to mRNAs in terms of their composition thanks to some common properties between them which include the 50-capping, (poly-A), splicing, and RNA-polymerase II acts by a copy for the lncRNAs molecules from specific portions of the genome such as remote protein-coding, exonic, and intergenic[15].

The biogenesis of lncRNAs is monitored via some exciters and processes that are formed for each level according to the cell type, as most of them have diverse expression modes, have featured nuclear positions, and receive transfer processes within and between cells, as well as post-transcriptional adjustments [50]. To create variety in proteins, lncRNAs are likely to perform alternative splicing between some specific genes by reacting with some factors and forming a double structure with pre-mRNA and thus re-forming chromatin [51]. When the transcription process is completed, the lncRNAs molecules are tucked into a double structure that contains some regions that enable them to interact, conjugate, and perform binding or modification operations between them and with RNAs such as mRNAs and miRNAs, as well as proteins, DNA and other types of lncRNAs [52].

6. REGULATION OF LONG NON-CODING RNAS TRANSCRIPTION

Because lncRNAs have originated as valuable actors in regulating the expression and also have a greater level of specificity, i.e., they are displayed in a type of cell, tissue, growth conditions [1], or disorder state-particular mode, quantitative variances in the transcriptional regulation of lncRNAs or mRNAs indicate that lncRNAs have been particularly regulated like a category [22].

The selectivity is often used to argue that lncRNAs expression is far more closely controlled than of protein-coding genes, inclusion of the lncRNAs plays a critical role in cell state determination [53]. In mammals, lncRNAs stimuli are about as evolutionarily preserved as mRNAs stimuli, and lncRNAs expression patterns are frequently associated with mRNAs expression fashions including both trans-NATs and cis-NATs indicating the significance of lncRNAs expression programs and proposition that they may be co-regulated in expression links [54].

Generally, small or long non-coding RNAs participate in numerous regulatory actions in the transcriptional and post-transcriptional development, and also in the epigenetic stages [55], therefore they can be involved in a wide range of biological and chemical regulatory mechanisms, which would include protein and gene regulation, nuclear functional arrangement, RNAs cloning, chromatin arranging, and cellular construction protection [56–58].

lncRNAs have numerous activities at the transcriptional stage, including disrupting transcriptional material attachment to particular coding domain, adjusting

transcriptional component location mostly in sequence, interfering for internal RNAs, and generating scaffolding with proteins and DNA [59], in addition are acting as molecular indication, sponges for miRNAs reservation, and ribonucleoprotein compound conductor [60]. The regulations and activities of lncRNAs in the post-transcriptional stage include the mRNAs adjusted via substitution splicing and modify the influences of mi-RNA on particular gene, either immediately or secondarily [61]. Also, nuclear lncRNAs such as metastasis-associated lung adenocarcinoma transcript-1(MALAT1) and nuclear enriched abundant transcript-1 (NEAT1) engage an important function in the regulation processes at post-transcriptional stages through responses for the mRNA splicing and protein-coding[62, 63].

7. CONCLUSION

lncRNAs have many characteristics and functions that are involved in many biological systems, which motivated researchers to study and investigate the pathways in which they participate. Despite the ongoing discoveries of new transcripts of lncRNAs among mammalian genes, it was important to review the biogenesis of lncRNAs and the main groups of these genes and recognize the most important types of them based on the genetic location, structural, and functional that enabled them to participate in the regulatory and biological activities for the genetic factors and the control of many diseases in the body. Thus, the continued diversity of lncRNAs requires the development of new techniques and methodologies that help improve the discovery of new transcripts and understand their diverse biological functions related to the development of human diseases.

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الخلاصة :

الحمض النووي الريبوزي الطويل الغير مشفر (lncRNAs) عرف منذ وقت ليس ببعيد كنوع من أنواع الاحماض النووية الريبوزية الغير مشفرة والمتنوعة والتي حصلت على الكثير من الاهتمام بسبب أنشطتها التنظيمية المتعددة على المستوى النووي والخلوي ومشاركتها المهمة في تنظيم العديد من الفعاليات الكيميائية والبيولوجية. على الرغم من أن (lncRNAs) يتم التعبير عنها بمستويات قليلة، ولا تقوم بترميز البروتينات، ويتم حفظها بشكل غير كافٍ، ويمكن أن تعمل بمجموعة متنوعة من الآليات، لكنه تم اكتشاف بعض الخصائص والوظائف لعدة نسخ من (lncRNAs) تفصلها عن الأشكال الأخرى من الحمض النووي الريبوزي الغير مشفر. سننظر هنا عن كيفية تطور الأحداث في (lncRNAs) ونتحدث عن الخصائص الرئيسية والتأثيرات البيولوجية، وكذلك كيفية تحقيق مثل هذه المجموعة الواسعة من الوظائف باستخدام مجموعة متنوعة من الآليات مثل نقل البروتين، نسخ الجينات، إعادة ترتيب الكروماتين، الخصائص الفريدة وغيرها من الانشطة البيولوجية.