Chapter 4

Roles of Non-Coding RNAs in Transcriptional Regulation

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Abstract

Non-coding RNAs (ncRNAs) are functional RNA molecules that are transcribed from mammalian genome but lack protein coding capacity. Nearly 80% of the human genome constitutes non-coding elements such as small non-coding RNAs, sncRNAs (miRNA, piRNA, SiRNA, SnRNA) and long non-coding RNAs, lncRNAs (linc RNA, NAT, eRNA, circ RNA, ceRNAs, PROMPTS). These ncRNAs have been extensively studied and are known to mediate the regulation of gene expression. In recent decades, lncRNAs have emerged as pivotal molecules that participate in the post-transcriptional regulation by acting as a signal, guide, scaffold and decoy molecules in addition to their role(s) in transcription. ncRNAs are known to play critical roles in defining DNA methylation patterns, imprinting as well as chromatin remodeling, thus having a substantial effect in epigenetic signaling. The expression of lncRNAs is regulated in a tissue specific and developmental stage specific manner and their mis-regulation is often associated with tumorigenesis. Henceforth, this chapter focuses mainly on the role(s) of ncRNAs in transcriptional and post-transcriptional regulation and their relevance in cancers.

Keywords: lncRNAs, miRNAs, DNA methylation, epigenetic signaling, transcriptional regulation, cancer

1. Introduction

1.1. The incredible RNA molecules

According to "RNA world hypothesis", early life was started with RNA molecules. Later with time, storage of information evolved to more stable DNA and RNA which emerged as a

messenger of stored information thereby completing the central dogma of life. Though 80% of the human genome is transcribed into RNA, majority of RNA lacks protein coding potential and referred as "non-coding RNA" (ncRNA). Further, genome sequencing technologies have revealed that the mammalian transcriptome is much more complex and their transcription is regulated by developmental stages [1]. The continuing discovery of new classes of regulatory ncRNAs suggests that RNA has continued to evolve along with proteins and DNA.

ncRNAs are divided into two major groups based on an arbitrary threshold of 200 nucleotides (nt) namely short ncRNAs (sncRNA) and long ncRNAs (lncRNAs) (**Figure 1**). sncRNAs include functional RNAs such as t-RNAs, r-RNAs and snRNAs which are involved in transcriptional and translational regulation. In addition to these conventional RNAs, short ncRNAs also include different regulatory RNAs such as microRNAs (miRNAs) [2, 3], small interfering RNAs (siRNAs) and P-element-induced wimpy testis (PIWI) interacting RNAs (piRNAs) [4], all of which regulate gene expression. In contrast to sncRNAs, the lncRNAs are a group of large, heterogeneous ncRNAs of unknown function. Similar to coding RNA transcripts, lncRNAs contains epigenetic marks indicating their ability to express differentially [5] and the presence of introns in lncRNAs emphasizes the existence of splice variants. These lncRNAs exist in both polyadenylated and non-polyadenylated forms and hence are termed "bimorphic" [6]. LncRNAs include many different types of RNA and exhibit a wide range of secondary and tertiary structures compared to the coding transcriptome. Some pseudogenes and

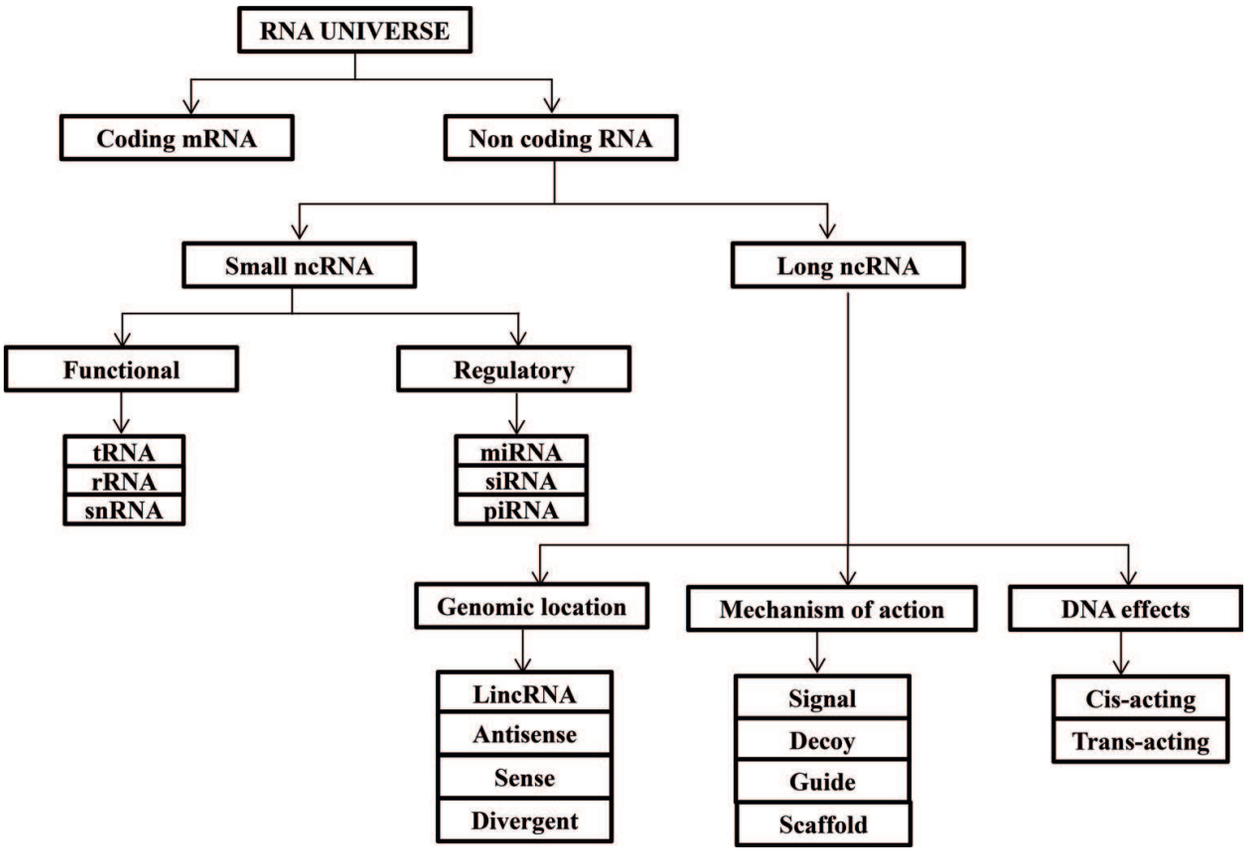

Figure 1. Classification of non-coding RNA (ncRNA).

copies of coding genes harboring mutations render lncRNAs non-coding [7]. Many lncRNAs are known to overlap coding genes [8]. A lncRNA might encompass either the entire gene or only a part of it and these lncRNA may originate from either the sense or antisense strand [9, 10]. The lncRNAs were termed based on their mechanism of action, such as intergenic (lincRNA), natural antisense transcripts (NATs), enhancer RNA (eRNA), circular RNA (circRNA), promoter associated long RNA (pRNA), etc. LncRNAs act at different levels of gene expression to exhibit diverse cellular functions. This functional diversity reflects the versatility of ncRNA and its interaction with a large number of substrates in a highly specific manner. Moreover, the expression of ncRNA is dynamic and can be rapidly up-regulated or down-regulated during developmental stages or differentiation without being translated [11]. Henceforth, in this chapter, we will discuss mainly on the gene regulatory roles of lncRNAs and miRNAs in distinct cellular functions and developmental regulation.

2. The small non-coding RNAs (sncRNAs)

The sncRNAs are extensively studied in the last decade and have been associated with RNA interference (RNAi) pathways, which lead to silencing of specific genes and protection of the cell or genome against viruses, mobile repetitive DNA sequences, retro-elements and transposons [12].

2.1. miRNAs and siRNAs

Both the siRNAs and miRNAs are 20–30 nucleotides long and generated from sense and antisense DNA strands, pseudogenes and inverted repeats. These molecules induce mRNA degradation or translational repression, which in turn result in the alteration of gene expression. About 60% of translated protein coding genes are negatively regulated by miRNAs [13]. Some transcripts are regulated by a single miRNA, while others are regulated by more than one miRNAs [14]. In addition to the transcriptional gene regulation, miRNAs play important roles in pivotal biological processes such as cell proliferation, cell differentiation, development, and cell death [15–18].

2.2. miRNA and siRNA biogenesis and mechanism of action

The process of miRNA biogenesis is quite characteristic for the ncRNAs subclass. Based on cellular requirement, the primary miRNA transcript (pri-miRNA) is first transcribed from the DNA by RNA polymerase II and characterized by one or many stem-loop hairpins which encompass the functional mature miRNA in their stem. In animals, the first step occurs in nucleus, in which the pri-miRNA upon recognition by two nuclear enzymes, Drosha and DGCR8 is processed into dsRNA molecule containing one or more hairpins of approximately 70 nucleotides long, which are called as precursor miRNAs (pre-miRNAs). Then they are exported to the cytoplasm by the nuclear export protein exportin-5 [19]. In cytoplasm, the pre-miRNA is recognized and processed by the RNase III enzyme, Dicer which removes the hairpin loop resulting in 20–23 nt dsRNA (miRNA-miRNA*) molecule. In case of siRNAs, the small RNA

duplex molecules produced by the action of Dicer, creates a RNA duplexes with 2-nt overhangs at their 3′ ends and phosphate groups at their 5′ ends [19]. Only one of the two strands of dsRNA acts as a guide strand and directs gene-silencing while, the other strand incorporates into the RNA-induced silencing complex (RISC) containing the Argonaute proteins (Ago1/2) and the GW182, where the anti-guide or passenger strand is degraded resulting in 20–23 nt mature miRNA (**Figure 2**). The siRNAs are recognized by Argonaute protein 2 (Ago2) [18, 20], and the selection of the different Ago proteins are based on the small interfering RNA duplex structure. Generally, siRNAs that are perfect duplexes in terms of base pairing are loaded into Ago2, whereas duplexes presenting mismatches as in the case of miRNAs, are driven by Argonaute 1 (Ago1) [21, 22]. When the complementarity between the miRNA bound to Ago1 and the target m-RNA is high, miRNA tailing and 3′–5′ trimming occurs. The discrimination between Ago1 and Ago2 depends on the action of Hen1; an enzyme that adds the 2′-*O*-methyl group at the 3′ ends of small RNAs bound to Ago2, but not those bound to Ago1 [23]. This methyl group is known to block tailing and trimming of the miRNA. The RISC complex then targets the mRNA transcript based on sequence complementarity between the

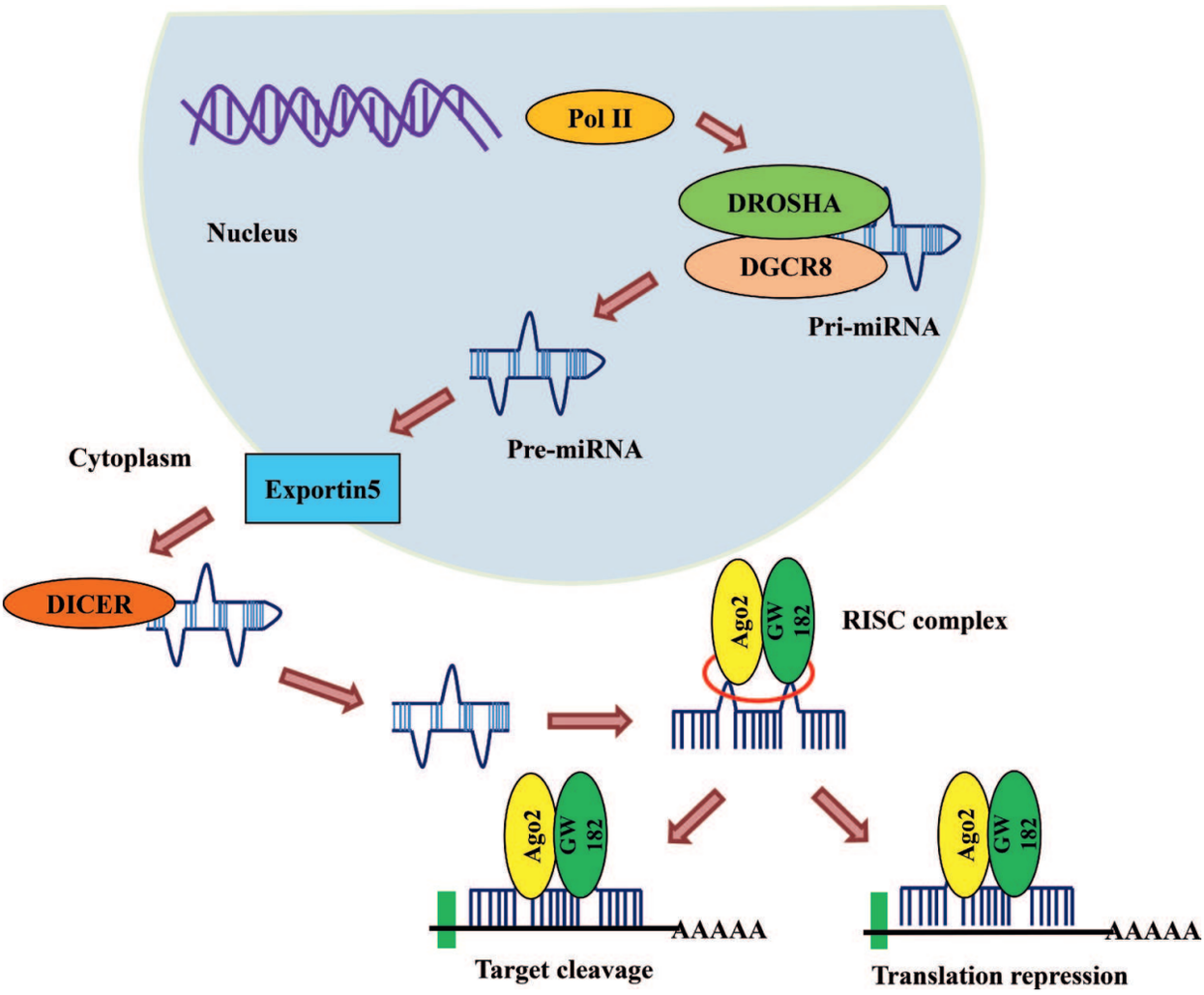

Figure 2. Biogenesis of miRNA and its mechanism of action (modified from Hrdlickova B *et al*. [18]).

miRNA sequence and nucleotides in the 3′ untranslated regions (3′ UTR) of the target mRNAs [24]. The binding of the RISC complex to its target leads to direct Ago-mediated cleavage of the target and causes mRNA degradation if the homology between miRNA and its target mRNA is extensive or to deadenylation followed by translation prevention if the homology between the miRNA and its target is less extensive [20, 25]. Efficient targeting requires continuous base pairing of the miRNA seed region (which is a stretch of 6–8 nucleotides of the mature miRNA) with its target mRNA [25, 26]. Unlike miRNA, siRNA base pairs perfectly and induce mRNA cleavage only in a single specific target. Initially, it has been showed that miRNAs mainly target the 3′ UTRs of mRNAs [20], but recently, it was found that miRNA target sites also been located in the 5′ UTRs and even in coding regions of some of the target mRNAs [20, 27]. For example, mir-148 targets on the coding regions of DNMT3B.

2.3. Role of miRNA in cancer and diseases

miRNAs have been shown to be involved in several human diseases including cancer, neurodegenerative, cardiovascular and autoimmune diseases [14]. Differential expression of specific miRNA will result in the up-regulation or down-regulation of their targets leading to the deregulation of cellular pathways.

In human diseases, expression of miRNAs could be differentially regulated by:

i. Altered functions of the enzymes involved in the miRNA biogenesis pathway. For example, DiGeorge syndrome results due to haploinsufficiency of DGCR8 [18].

ii. Transcriptional repression of miRNAs by promoter hypermethylation [28]. For example, the miR-200 family is involved in the control of the epithelial-mesenchymal transition (EMT) [18].

iii. Genetic alterations in miRNA genes or in their regulatory motifs which can have deleterious consequences [29]. The deletion of chromosome 13q14 in chronic lymphocytic leukemia (CLL) patients is the best studied example in which the deleted area contains the miR-15a and miR-16-1 genes that target the anti-apoptotic/pro-survival gene BCL-2 (B-cell lymphoma 2) and thus deletion of this region contributes to the greater survival of cancerous cells [18].

3. The long non-coding RNAs (lncRNAs)

LncRNAs are defined as a heterogeneous group of transcripts that are >200 nucleotides (nt) in length. These lncRNAs do not exhibit coding potential [30–32] and are transcribed from DNA. These lncRNAs can be intergenic, exonic, in enhancer regions or in the regions distal to protein-coding genes [11, 33]. Like mRNAs, lncRNAs are transcribed by RNA polymerase II (RNA PolII) and undergo post-transcriptional processing such as alternative splicing, 5′ capping, polyadenylation and RNA editing and also carry single nucleotide polymorphisms (SNPs) [31, 34].

In comparison to protein coding RNAs, lncRNAs have few, but longer exons [30, 35]. Other characteristics of lncRNAs include: (i) well conserved lncRNA promoter regions between vertebrates; (ii) unique promoters, DNA-binding motifs and preferred transcription factors (TFs), (iii) less conserved lncRNA exons between species and (iv) tissue specific expression profiles [5, 31, 36–38]. Compared with protein coding genes, only 11–29% of lncRNAs are ubiquitously expressed in all tissues and they are expressed at very minimum levels [31, 39]. Computational analysis of RNA-Seq data has suggested that lncRNA transcription is independent and influence the transcription of neighboring protein coding genes [31, 38]. The origin of lncRNAs is still under debate. A recent study [40], has reported that more than two-thirds of mature lncRNA transcripts contain transposable elements (TEs). This observation has led to the postulation that the majority of lncRNAs might have arisen via insertion of TEs [41].

3.1. Classification of lncRNAs

LncRNAs have been classified based on their: (i) genomic location, (ii) mechanism of action, and (iii) effects on DNA sequences.

3.1.1. Classification of lncRNAs based on genomic location

LncRNAs could be classified into four broad categories based on their relative position to the nearest protein coding genes (**Figure 3**). The first class is the "long intergenic non-coding RNAs" (lincRNAs) which is the largest group of lncRNAs and these genes do not overlap or lie in close proximity to protein coding genes [5, 42]. The second most prevalent class of lncRNA is the "antisense lncRNA" that is transcribed from the antisense strand and are overlapping. Based on their overlap, the antisense lncRNAs are subdivided into two:(i) "intronic antisense lncRNAs" where the lncRNA transcript falls completely within the boundaries of an opposing intron, and (ii) "natural antisense transcripts" (NATs) which partially overlaps around the promoter or at the terminator site of the coding gene [43, 44]. The third class of lncRNAs comprises the "sense lncRNA" transcripts which can be "sense intronic or "sense overlapping." Such transcripts are located on the same strand and transcribed in the same direction as a protein coding gene. The fourth class of lncRNAs is the "bidirectional lncRNAs" or "divergent lncRNAs." These transcripts are located on the antisense strand and have their transcription start site (TSS) close to the TSS of the protein-coding gene, but are transcribed in the opposite direction [45–47].

3.1.2. Classification of lncRNAs based on their mechanism of action

LncRNAs can interact with DNA, RNA as well as proteins. LncRNAs have been implicated mainly in post-transcriptional gene regulation by controlling processes like protein synthesis, RNA sequestration, RNA transport and have been shown to control transcriptional gene silencing via epigenetic regulation and chromatin remodeling [48, 49]. LncRNAs are divided into four archetypes based on their molecular mechanism (**Figure 4**) [18]. LncRNAs that belongs to the "signaling archetype" acts as a molecular signal for a particular biological condition and may activate or silence the genes depending on the stimulus (**Figure 4A**).

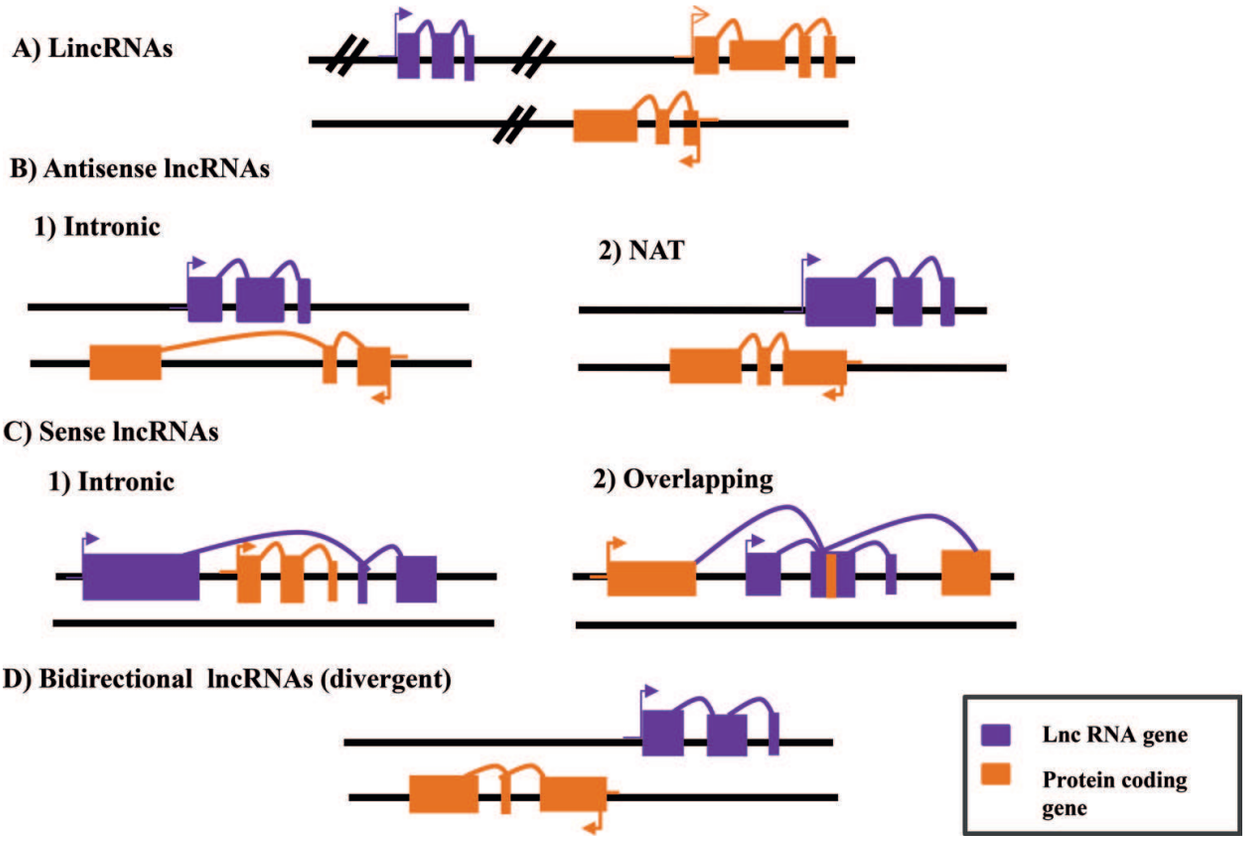

Figure 3. Classification of lncRNAs based on position relative to the nearest protein coding gene (modified from Hrdlickova B *et al*. [18]).

Some of the examples of lncRNAs displaying the signaling archetype are lncRNAs involved in embryonic development (HOTAIR and HOTTIP), DNA damage response (lincRNA-p21 and PANDA), stress responses (COLDAIR and COOLAIR), etc. [18]. The second category is the "decoy archetype" where the lncRNAs act as decoys that bind to and interfere with the function of other RNAs or proteins. They act by competing with their sequences or structures for binding and are considered to be negative regulators (**Figure 4B**). For example, PANDA binds to the transcription factor NF-YA and prevents the activation of NF-YA induced pro-apoptotic targets [18]. The "guide archetype" is the third class, in which the lncRNAs binds to specific proteins and transport them to the specific targets. The interaction may be direct (between lncRNA-protein complex and the DNA) or indirect (between lncRNA-protein and protein-DNA complexes) (**Figure 4C**). These lncRNAs may interact as activators or repressors with neighboring (cis-acting) or distant (trans-acting) genes. Examples of lncRNAs employing this mechanism are HOTAIR, lincRNAp21, Xist, COLDAIR and Jpx (just proximal to XIST). The fourth archetype is "scaffold archetype" (**Figure 4D**), where the lncRNAs act by bringing the bound proteins into a complex or in spatial proximity. Examples of this lncRNAs are ANRIL (antisense ncRNA in the INK4 locus) which functions as a scaffold for the chromatin remodeling complexes PRC1 and PRC2, HOTAIR (scaffold for PRC2 binding it to the LSD1 complex) and TERC (telomerase RNA component) that scaffolds the telomerase complex [18].

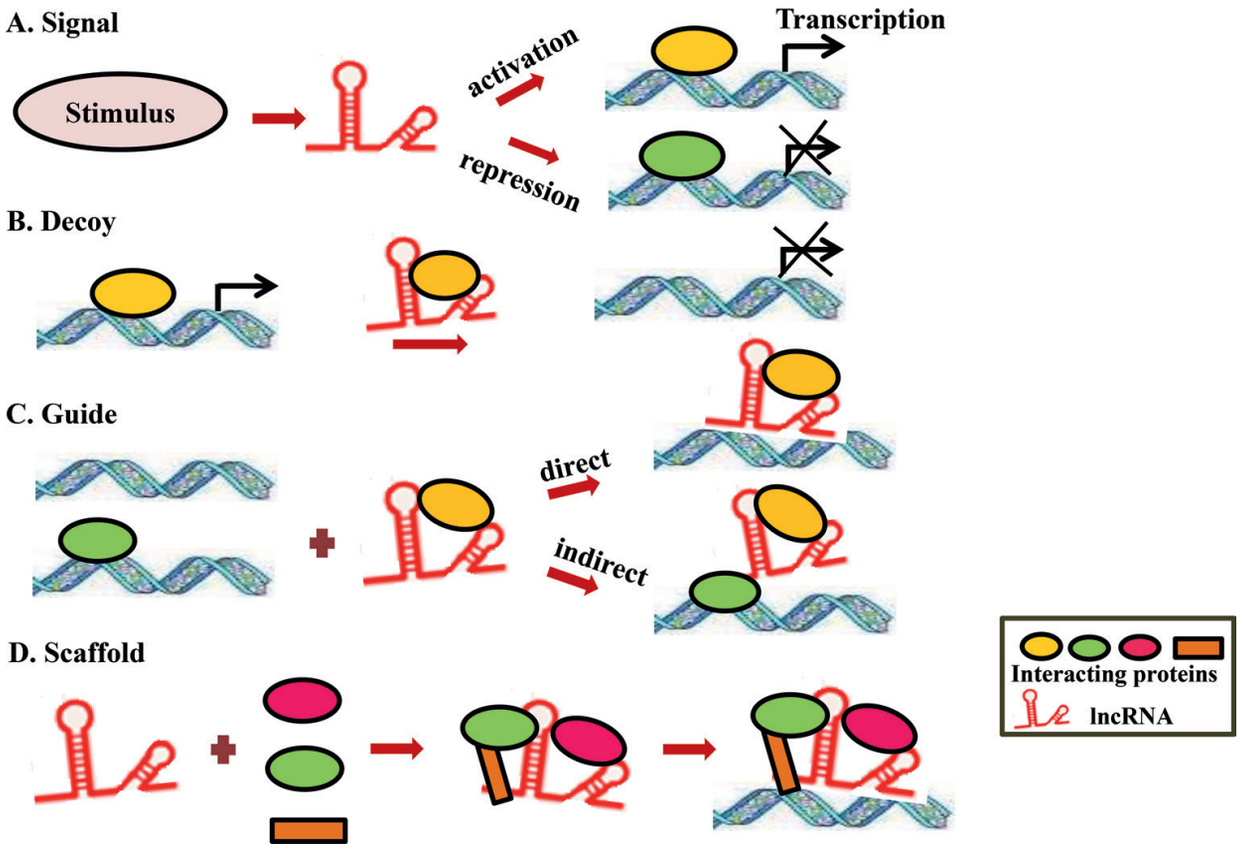

Figure 4. Classification of lncRNAs based on the mechanism of action.

3.1.3. Classification of lncRNAs based on their effects on DNA sequence

LncRNAs could be divided into "cis-acting" and "trans-acting" based on the effects exerted on DNA sequences. The effects of cis-acting lncRNAs are restricted to genes in close genomic proximity (usually the genes in the chromosome from which they are transcribed from), whereas trans-acting lncRNAs affect distant genes (the genes on other chromosomes) [50]. The action of both cis and trans lncRNAs is locus specific and in both cases, the lncRNA binds epigenetic modifiers through a specific sequence or structure and targets them to promoter regions to regulate the expression of respective genes. For example, HOTTIP and HOTAIR lncRNAs [51]. The major example of general cis-regulation is induction of X inactivation by the Xist lncRNA in female mammals. Xist is expressed from one of the two X chromosomes and induces silencing of the whole chromosome [50]. Example of trans-regulation is the B2 lncRNA that binds to RNA PolII and inhibits phosphorylation of its carboxy-terminal domain (CTD), thus affecting RNA polymerase reaction [50].

4. Gene regulation by lncRNAs

LncRNAs have diverse regulatory functions and might regulate gene expression by modulating chromatin remodeling, cis and trans gene expression, gene transcription, post-transcriptional

regulation, translation, protein trafficking and cellular signaling [33, 34]. Growing number of evidences implicate lncRNAs in transcriptional gene regulation, thereby suggesting a significant role(s) for lncRNAs in such tightly regulated process [52, 53]. The mechanisms of transcriptional and post-transcriptional regulation by lncRNAs is discussed below.

4.1. Transcriptional regulation

Regulation of transcription is considered to be an interplay of transcription factors (TFs) and chromatin modifying factors at the gene promoters. LncRNAs modulate gene expression by specifically associating with other molecules; DNA, RNA and protein, either at the promoters or at the enhancers of their target genes. LncRNAs regulate transcription by various mechanisms and some are shown below.

4.1.1. Enhancer RNAs

Enhancer RNAs (eRNAs) are a category of lncRNAs derived from enhancer regions of genes, which interact with DNA to upregulate gene transcription through two possible mechanisms such as enhancer-promoter looping and tracking of transcriptional machinery [54]. While studying the enhancers activated by calcium signaling in mouse neurons, Kim et al. for the first time, identified a eRNA of about 2 kb transcribed bidirectionally from active enhancers. The expression of this eRNA correlated with the activity of the enhancer region [55, 56], which suggests that eRNAs contribute to enhancer function and influence the transcription of genes.

4.1.2. Activating ncRNAs

Activating ncRNAs are a class of lncRNAs which are transcribed from independent loci, but not from enhancers and have a transcriptional activation function [57, 58]. Activating ncRNAs specifically activate the transcription of neighboring coding genes in an RNA-dependent fashion, and require the activity of the coding gene promoter [58]. These activating ncRNAs are functionally similar to eRNAs. However, in contrast to eRNAs, activating ncRNAs are spliced, polyadenylated stable transcripts. Gene activation mediated by the activating ncRNAs requires a change in chromosomal conformation to bring the activating ncRNAs locus close to the promoter of its target gene [59]. A number of activating ncRNAs have been shown to be associated with the mediator complex which is involved in bridging promoters with enhancers; and depletion of this complex inhibits looping between the activating ncRNAs locus and its target gene. Thus, eRNA and activating ncRNAs function by interacting with the same set of molecules, forming a scaffold for a protein complex that bridges the enhancer-like element and the promoter of a coding gene (**Figure 5**) [60].

4.1.3. Transcriptional regulation by recruitment of chromatin modifiers

As discussed earlier in this chapter, lncRNAs mediate epigenetic changes by DNA methylation, histone modification and by recruiting chromatin remodeling complexes to specific genomic loci mainly to the promoter regions and causes repression or activation of the target genes. It

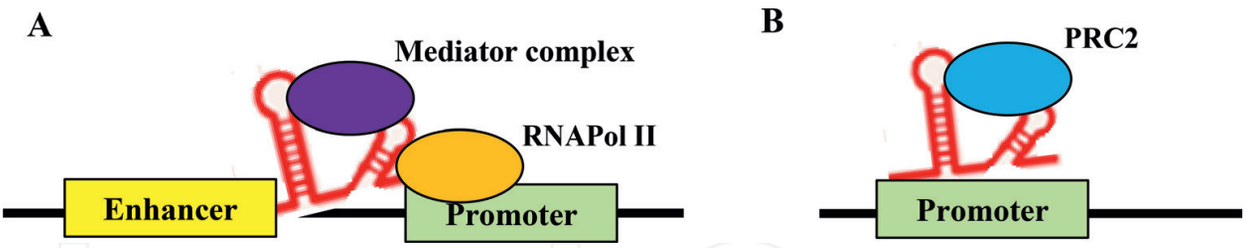

Figure 5. Models of transcriptional regulation. (A) Bridging scaffold model: lncRNAs (red line) transcribed from enhancer-like non-coding genes are required to recruit the mediator complex. (B) Tethered scaffold model: lncRNA (red line) recognizes specific DNA motifs and recruits histone modifying enzymes.

was found that the lncRNA might serve two functions. (i) lncRNAs act as a bridging scaffold and binds to a protein or protein complex to facilitate chromatin conformational changes [61]. (ii) lncRNAs act as tethered scaffold that targets chromatin modifying enzymes to specific DNA motifs (**Figure 5**). For example, the lncRNA HOTAIR (Hox transcript antisense RNA) acts as an epigenetic-protein scaffold and possess multiple binding domains for distinct proteins. At the 3′ end, HOTAIR contributes to the demethylation of H3K4 by interacting with lysine-specific histone demethylase 1A (LSD1), restrictive element 1-silencing transcription factor (REST), and REST corepressor1. At the 5′ end, *HOTAIR* originated from the *HOXC* locus and causes transcriptional gene silencing across 40 kb of the *HOXD* locus in *trans* by inducing a repressive chromatin state, by recruitment of the Polycomb chromatin remodeling complex PRC2 and reinforcing H3K27 methylation [34, 62].

4.1.4. Genomic imprinting and X-chromosome inactivation

Genomic imprinting is the phenomenon of epigenetic silencing of an allele inherited from either of the parents [63]. Imprinting Control Regions (ICRs) are short stretches of DNA that play a critical role in imprinting of multiple genes [64]. Interestingly, it has been observed that the imprinted regions show significant association with ncRNAs, which mediate the silencing by diverse mechanisms like chromatin remodeling and enhancer competition [65]. X chromosome inactivation is a process mediated by the long ncRNA- *Xist,* in which one copy of the X chromosome in females is inactivated. From the *Xist* locus, a small internal non-coding transcript *RepA* recruits PRC2 to silence one X chromosome [61]; whereas PRC2 is formed from the remaining active X chromosome by the antisense transcript *Tsix*. However, an alternative mechanism is described by another study in which *Xist* and *Tsix* anneal to form an RNA duplex that is processed by Dicer to generate small interfering RNAs (siRNAs) which are required for the repressive chromatin modifications on the inactive X chromosome [1].

4.2. Post-transcriptional regulation

At post-transcriptional level, lncRNAs regulate by acting as competing endogenous RNAs that regulate microRNA levels which in turn modulate mRNA levels by altering mRNA stability, mRNA decay, and translation [66].

4.2.1. LncRNA as a source of miRNA

Most pri-miRNAs are generally greater than 1 kb in length [67]; and therefore may be regarded as a form of lncRNA. There are two major sources of pri-miRNAs in the genome: (i) pri-miRNAs that are embedded within another gene and whose expression is usually but not always linked to the expression of the parent transcript, and (ii) pri-miRNAs that are transcribed independently from miRNA genes which contain promoters that regulate their transcription mainly by RNA polymerase II (RNA PolII) in a manner similar to mRNA [66]. Approximately 50% of miRNAs are produced from non-coding transcripts [68]; however, with miRNAs embedded in coding genes many miRNAs are also located within introns of non-coding genes (**Figure 6**) [66]. Such a genomic organization suggests that the host lncRNA does not simply act as a pri-miRNA but may have other additional roles encoded by the exons. For example, DLEU2 is the host gene of the tumor suppressor miRNA, miR-15a/16.1 cluster located within its third intron [66].

4.2.2. LncRNA as a negative regulator of miRNA

miRNAs are known to act as negative regulators of gene expression. Transcripts are targeted through binding of a short 6–8 nt seed sequence within the miRNA to a miRNA response element (MRE) in the 3′ UTR regions of targets. Computational predictions based on miRNA seed sequences found that many lncRNAs contain miRNA binding sites. This raises an interesting possibility that many lncRNAs function to regulate gene expression by sequestering miRNAs, thus limiting their concentration within the cell and thereby reducing the pool of available miRNA in the cell. In this way, the lncRNA acts as a negative regulator of miRNA function and thereby a positive regulator of gene expression. This is known as the "competing endogenous RNA (ceRNA)" hypothesis (**Figure 7**) [69, 70]. For example, the intergenic lincRNA-ROR, which inhibits miR-145 in pluripotent embryonic stem cells [66]. Competitive endogenous RNAs (ceRNAs) are lncRNAs that sequester miRNAs and inhibit miRNA functions and have two structurally distinct forms such as linear and circular. Non-circular or linear lncRNAs are single-stranded molecules that bind to miRNAs and regulate gene expression by promoting it to degradation [71]. Circular RNAs (circRNAs) are a type of ring-forming lncRNA that form

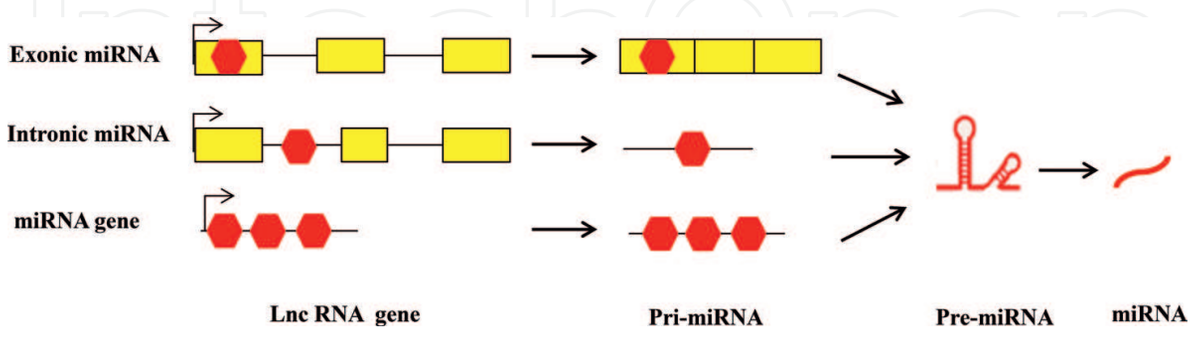

Figure 6. LncRNA as a source of miRNA. LncRNA genes contain embedded miRNA sequences (red hexagonal boxes) which may be located within an exon (orange box) or an intron (line) or occur in clusters within the genome. Though the sources are different, the pathways converge at the level of pre-miRNA structure which produce miRNA (modified from Dykes IM *et al*. [66]).

by linking the 3′ and 5′ ends with a back splicing covalent bond [72, 73]. In addition, lncRNAs can facilitate the inhibition of mRNA translation or decay by partial base pairing with the 3′ UTR sequences through their Alu elements in Staufen-mediated manner [74]. A non-coding transcript that shares a high degree of homology with a coding gene is likely to share many of its MREs and therefore pseudogenes are considered as good candidates to act as ceRNAs [7, 75, 76]. Example of such lncRNA include a pseudogene homologous to the gene encoding tumor suppressor phosphatase and tensin homolog (PTEN), which contains multiple MREs with in the 3′ UTR shared with the coding gene [76].

4.2.3. LncRNA-mediated and miRNA-independent mRNA degradation

In addition to regulating gene expression through interaction with miRNAs, some lncRNAs directly targets mRNA for degradation. For example, Staufen 1 (STAU1) is a protein that recognizes a specific motif in the 3′ UTR of mRNAs and mediates their degradation by nonsense mediated mRNA decay (NMD) [77]. STAU1 binds to a double-stranded RNA motif within the 3′ UTR of the mRNA encoding ADP-ribosylation factor 1 (ARF1), where it forms a stem loop structure. However, some mRNAs targeted by Staufen-mediated decay, lacks the stem loop structure and contains only a single stranded binding site within the 3′ UTR, e.g., serpin peptidase inhibitor-clade E member1 (SERPINE1). Interestingly, such mRNAs are targeted by a lncRNA carrying a complementary single stranded binding site and imperfect binding of lncRNA to the mRNA create a double-stranded RNA binding motif for STAU1. This class of lncRNAs are called as half STAU1 binding site RNAs [74].

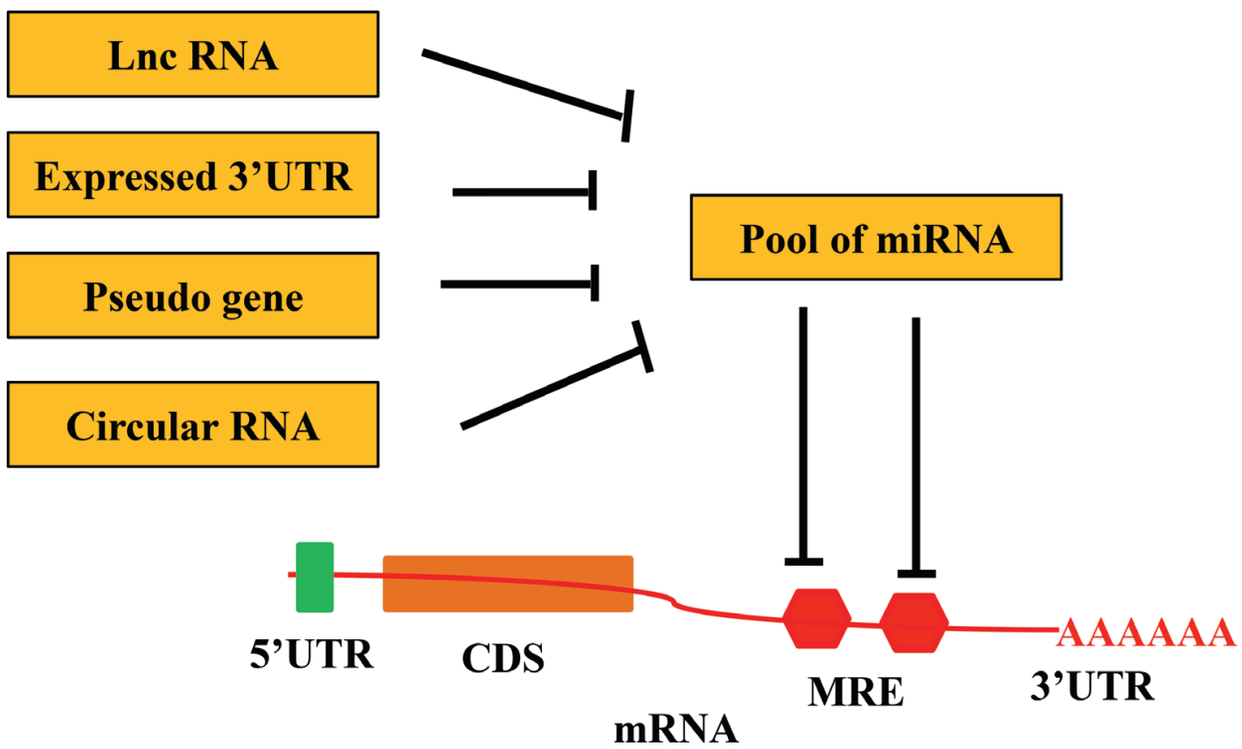

Figure 7. The ceRNA hypothesis. miRNA binds to identical MREs (hexagonal) which are usually present in a number of ncRNA species such as pseudogenes, circRNAs and other forms of lncRNAs and independently transcribed mRNA 3′UTRs. All of these RNAs compete for a limited pool of miRNA, thus positively regulating gene expression.

5. Roles of LncRNA in diseases

5.1. LncRNAs and aging

Aging is a complex physiological phenomenon with a progressive decline in functional capacities and environmental adaptations. The expression of lncRNAs is known to be affected during aging process and in turn, many lncRNAs govern major senescent pathways and senescence-associated secretory phenotype [78–80]. In human fibroblasts, senescence-associated lncRNA-SAL-RNA1 delays senescence and reduced levels of this lncRNA enhances senescence traits such as enlarged morphology, increased p53 levels and positive β-galactosidase activity [81]. Another example is the lncRNA MIR31HG, which is upregulated in oncogene-induced senescence, and its knockdown promotes a strong tumor-suppressor p16-dependent senescence phenotype [82].

5.2. LncRNAs in cancer and other diseases

Altered lncRNA function is identified as one of the causes for the dysregulation of gene expression which leads to several human diseases including cancer. One such lncRNA is MALAT1 also known as NEAT2, (nuclear-enriched abundant transcript2) which was identified as a predictive biomarker for metastasis development in lung cancer [83, 84]. It acts by inducing the expression of metastasis-associated genes [85]; and recently it was shown that in vitro metastasis of EBC-1 cells (human lung cancer cells) can be inhibited by antisense oligonucleotides directed to MALAT1 [85, 86]. Another example is lncRNA HOTAIR that interacts with PRC2 and alters chromatin to a metastasis-promoting state [87]; and causes cancers such as breast, colon, colorectal, gastrointestinal, pancreatic and liver cancer [88–91]. The lncRNAs αHIF (antisense to hypoxia inducible factor α (HIFα)) and tie-1AS (tyrosine kinase containing immunoglobulin and epidermal growth factor homology domain-1 antisense) are known to induce angiogenesis [42, 92]. PCGEM1 (prostate-specific transcript 1), UCA1 (urothelial cancer associated 1), SPRY4-IT1 (SPRY4 intronic transcript 1) and PANDA are involved in suppressing apoptosis [93–95]. LncRNAs also have roles in other diseases like neurogenetic Angelman syndrome and Beckwith-Wiedemann syndrome (BWS) [96]. LncRNAs have also been associated with cardiovascular diseases and other neurological disorders such as BACE1-AS or BC200 in Alzheimer disease, HAR1 (human accelerated region 1 lncRNA) in Huntington disease and ATXN8OS (Ataxin8 opposite strand lncRNA) in spinocerebellar ataxia type 8 [96–98].

6. Conclusion

The highly diverse biological functions of lncRNAs reflect the versatility of RNA molecules in the cell. Studies on different classes of ncRNAs, their biogenesis and functional overlaps suggest their complexity and their ability to operate as an integrated and regulated network. In this chapter, we have highlighted different mechanisms of regulation of gene expression by lncRNAs at transcriptional and post-transcriptional level by their ability to interact with

enhancers, promoters, chromatin-modifying complexes and miRNAs. Due to environmental exposures, genetic mutations and other causes, deregulation of lncRNAs are associated with various human diseases such as cancer, neurological disorders like Alzheimer's disease, cardiovascular diseases, and autoimmune diseases. This chapter along with recent evidences emphasizes the significance of lncRNA as novel therapeutic targets in aging and aging-related human diseases.

7. Future perspectives

Mounting evidences suggest significant roles of ncRNAs in physiological and pathological processes, which have expanded our basic understanding of gene expression. However, on the other hand, we have also realized the increasing complexity in the structure and organization of genome and gene networks. Recently, our laboratory identified a novel non-coding RNA of DNMT3B variant (DNMT3B9) from leukemic cell lines and the exact roles in hematopoiesis study is underway. This chapter recommends future research on the structural motifs and gene regulatory network of ncRNAs and their stability and degradation process, which we believe will expand the horizons of ncRNAs biology to establish potential diagnostic and therapeutic strategies in this field. Another challenging avenue is to explore the mechanisms underlying the functions of ncRNAs, which still remain elusive. Also, studies on the interplay between various ncRNAs might shed light on the usage of ncRNAs as potential biomarkers for early detection and improve the treatment of various diseases including cancer. With increasing discovery of ncRNAs and advancing technologies, ncRNA based therapies would be an effective health-care strategy.

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