Non-coding RNA Era is Dawning

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Abstract

Vast majority of transcripts in eukaryotic organisms are non-coding RNAs (ncRNAs). Except for traditional non-coding transcripts ribosomal RNA (rRNA) and transfer RNA (tRNA), both of which play essential roles in protein translation, most of ncRNAs haven't been functionally characterized and appreciated. Accumulating evidence, however, suggests that ncRNAs take part in many biological processes, and abnormal expression and/or dysfunction of them may result in a variety of diseases in human, such as cancers, neurodegenerative diseases, cardiovascular diseases and genetic diseases. The current understanding and future potential of ncRNAs in regulation of chromatin dynamics and gene expression, and implication to diseases are briefly outlined here.

Introduction

Up to 90% of eukaryotic genomes are transcribed. Only ~2% of these transcripts encode proteins, while remaining 98% are ncRNAs [1,2]. ncRNAs can be categorized into infrastructural ncRNAs and regulatory ncRNAs. Constitutively expressed infrastructural ncRNAs include ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), small nuclear RNAs (snRNAs), and small nucleolar RNAs (snoRNAs). Based on their size, regulatory ncRNAs can be grossly classified into small (<200nt) ncRNAs encompassing small interfering RNAs (siRNAs), microRNAs (miRNAs), and Piwi-interacting RNAs (piRNAs), and long (>200nt) non-coding RNAs (lncRNAs) [2-4].

Certain members of infrastructural ncRNAs have well-characterized functions. For instance, rRNAs and tRNAs are integral for translation to take place in the cells. The snRNAs are components of spliceosomes, which carry out the splicing processes essential for removing intron sequences during mRNA maturation. The snoRNAs guide chemical modifications of rRNAs, and snRNAs [5,6].

In addition, it has been determined that siRNAs and miRNAs regulate gene expression on post-transcriptional level through RNA cleaving and translational inhibition respectively, whereas piRNAs silence transposable elements (TEs) or imprinted loci of the genome through DNA methylation and/or histone modifications transcriptionally, and mRNA degradation or translation inhibition post-transcriptionally [7-10]. In this commentary, recent evidence that ncRNAs contribute to the

maintenance of chromosomal structure, regulation of gene expression, and development of diseases will be highlighted.

ncRNAs and chromosomal structures

Telomeres are heterochromatic structures located on the ends of chromosomes, and protect the chromosomal DNA from being damaged. The highly repetitive nature of telomere regions causes them to be problematic in replicating, and thereby progressively shortened after each replication cycle, which is in turn overcome by the reverse transcribing enzyme telomerase. Recent studies demonstrated that eukaryotic telomeric ends are transcribed into lncRNAs named Telomeric Repeat containing RNAs (TERRA), which facilitate formation of telomeric heterochromatin, and inhibit telomerase from improperly lengthening the chromosomal ends [4]. Insufficient TERRA expression is correlated to breast cancer [11]. In early developmental stages of mammalian females, one of the pair of X chromosomes is transcriptionally silenced and condensed into a Barr body, and thereby provides equivalence between male and female in terms of products of genes sitting on X chromosomes (dosage compensation). X-inactive-specific transcript (Xist) is an lncRNA (17kb in human) transcribed from the inactive X chromosome, coats the chromosome in *cis*, and recruits Polycomb Repressive Complex 2 (PRC2) conferring H3K27me3, leading to inactivation. Xist is positively regulated by a group of lncRNAs arising from a region called X inactivation center (Xic), and negatively regulated by an antisense RNA, Tsix [12,13].

ncRNAs in gene regulation

Several lines of evidence suggest that lncRNAs may regulate protein-coding gene expression in post-transcriptional level and transcriptional level [14-17]. Post-transcriptional regulation could be accomplished through miRNA sponge action of lncRNAs, thereby miRNA effector complexes are titrated away from their mRNA targets. Consequently, the mRNAs are spared from repression and allowed to be translated [14,15]. lncRNAs might regulation transcription in *cis* or *trans*, and positively or negatively. lncRNAs act in *cis* when they affect genes situated in the chromosomes from which they are transcribed, while in *trans* when they affect genes located on different chromosomes.

One prototypical example of lncRNAs that act in *trans* is 331 nucleotide 7SK lncRNA, which halts transcriptional elongation by hampering the P-TEFb elongation factor from phosphorylating the RNA polymerase II carboxy terminal domain (CTD) [18]. Hox anti-sense intergenic RNA (HOTAIR) emanates from HOXC locus on chromosome 12, acts in *trans* to repress transcription around HOXD locus on chromosome 2 in human cells via targeting lysine specific demethylase1(LSD1) and PCR2, which can remove methyl groups from H3K4me2 and add methyl groups to H3K27 respectively, to the same genomic region [17,18].

As opposed to *trans*-acting lncRNAs, which depend on their RNA products to exert their influence, *cis*-acting lncRNAs may operate in two distinct fashions. While long-range (non-overlapped genes) regulation might entail their RNA products, the short range (overlapped genes) regulation could be carried out through 'transcriptional interference'(TI) where mere the procedure of lncRNA transcription is sufficient [12,17]. HOXA transcript at the distal tip (HOTTIP) is an ~3.7kb ncRNA transcribed from one end of the HOXA locus in mammalian cells, guides MLL1 (mixed lineage leukemia1) and WDR5 (WD-repeat containing protein5) histone modifying complex to promoter region of flanking genes via long range looping, and thereby causes trimethylation of H3K4 of the promoters and transcriptional activation of these genes [12,17,18]. Insulin-like growth factor type-2 receptor (Igf2r) is an imprinted gene, and silenced in paternal alleles [1]. Airn, a lncRNA expressed on paternally inherited chromosomes, overlaps the promoter of Igf2r gene in an antisense orientation, hinders the occupancy of functional RNA Polymerase II on Igf2r promoter in the context of open chromatin, leading to silencing of Igf2r gene [12,17].

ncRNAs and diseases

As with protein-coding genes, mutation of ncRNA genes or aberrant expression of ncRNAs can cause a variety kinds of diseases. In Huntington's disease, for instance, there is an imbalance of neural lncRNA repertoire in brain tissues. While taurine upregulated1(TUG1) and nuclear paraspeckle assembly transcripts (NEAT1) are upregulated, maternally expressed 3 (MEG3) is down regulated [19]. The SNP rs133049 in the lncRNA called antisense noncoding RNA in INK4 locus (ANRIL) is reported to associate with myocardial infarction and pharmacogenomic evaluation in hypercholesterolemia [20]. ANRIL has been shown to be excessively expressed in prostate cancer cells. So does HOTAIR in breast cancer [21-23]. It has been demonstrated that Xist is downregulated in female breast cancer, ovarian cancer and cervical cancer cell lines, and suppresses haematologic cancer in vivo in mice [23,24]. Obviously, ncRNAs have been implicated in various diseases, and have potential to serve as diagnostic markers or therapeutic targets.

Conclusion

In a nutshell, ncRNAs play crucial roles in all facets of biological processes in both cellular level and organism level. Abnormality of ncRNAs has been implicated in numerous kinds of diseases, and might serve as useful resources for the development of diagnostic and interventional pharmacology. It

is conceivable that more ncRNAs will be characterized in coming years, and ncRNA era is dawning.

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