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Noncoding RNAs and aging

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Abstract
In the recent years, novel regulatory functions of non-coding RNAs have been discovered. Non-coding RNAs (ncRNAs) are diverse classes of RNA molecules not translated into proteins that possess intricate regulatory and structural functions. The human genome sequencing performed by the International Human Genome Sequencing Consortium revealed that only 20–25,000 genes are protein coding, corresponding to less than 2% of the human genome (2004). Although the common belief that the remaining and larger portion of the human genome was not functional and considered as "junk DNA", recent studies based on tiling arrays and RNA deep sequencing show thousands of RNA transcripts not derived from known genes and not encoding proteins (KAPRANOV *et al.* 2007 ; CARNINCI *et al.* 2005). These molecules however are emerging as important and unexplored regulators of transcriptional, post-transcriptional, splicing and epigenetic processes. Among them, X chromosome inactivation (MEMILI *et al.* 2001) or genomic imprinting (SLEUTELS AND BARLOW 2002). In this review, I discuss recent developments in the field of ncRNAs and point toward a better understanding of how ncRNAs can affect aging processes.

Keywords: noncoding RNA (ncRNA), lncRNA, miRNA, aging, TGS and PTGS.

ncRNA classifications

They are diverse and range in size from around 21-22 nucleotides, such as microRNAs (BARTEL 2009), small nuclear RNAs and interfering RNAs (LAGOS-QUINTANA *et al.* 2001), to more than 10,000 nucleotides, such as X-inactive specific transcript RNA (Xist). ncRNAs can be categorized into various classes based on their biogenesis, size, and biologic function (see Table 1). There are two main groups: housekeeping non-coding RNAs (1) and regulatory non-coding RNAs (2). 1) Housekeeping ncRNAs include ribosomal, transfer, small nuclear, and small nucleolar RNAs, which are usually constitutively expressed. The short regulatory ncRNAs (<200 nucleotides) include miRNAs, siRNAs, and piwi-associated RNAs (piRNAs). In addition, long regulatory non-coding RNA (lncRNAs) (200–100,000 nucleotides) (GUTSCHNER AND DIEDERICHS 2012; PONTING *et al.* 2009) contribute to the regulation of gene expression at various levels, including chromatin modification, transcription and post-transcriptional processing.

MicroRNAs (miRNAs) are the best characterized class of short ncRNAs (19-24 nt), which are present in animals, plants, and algae (BARTEL 2009) (Table 1). They are transcribed as long transcripts by RNA polymerases II and III and then processed by a microprocessor complex (LEE *et al.* 2004; BORCHERT *et al.* 2006). Following export to the cytoplasm miRNAs are cleaved by Dicer protein and are loaded into the RNA-inducible silencing complex (IBANEZ-VENTOSO *et al.* 2006; KIM *et al.* 2009). These RNAs regulate the expression of target mRNAs at transcriptional (destabilizing target mRNAs) and translational (blocking translation) level (BARTEL 2004; DENLI *et al.* 2004). While in plants such regulation occurs through perfect base-pairing, usually in the 3' untranslated region (HUI *et al.* 2009) of the targeted mRNA, in mammals the base-pairing is only partial (LAGOS-QUINTANA *et al.* 2001; LEE AND AMBROS 2001).

piRNAs are small RNAs associated to PIWI-family proteins. piRNAs are produced by a long RNA, which is RNA polymerase II (Pol II) transcript. They are implicated in post-transcriptional gene regulation (Table 1),

they also provide an essential protection for germ-cell genomes against the activity of transposable elements (KAPRANOV *et al.* 2007) and in maintaining genomic integrity in somatic and germ cells (OKAMURA AND LAI 2008). They can play a significant role in protecting genomes against instability by repressing transposon activity via two important mechanisms: transcriptional gene silencing (TGS) and post (PTGS) (SIOMI *et al.* 2011; ROSS *et al.* 2014). The piRNAs differ from the rest of the ncRNAs in 2 aspects. While the others have 32 nt in length, these are generated from single-stranded RNA precursors through a Dicer-independent mechanism. In addition, piRNAs associate with PIWI proteins are germline-specific members of the Argonaute protein family. However, siRNAs and miRNAs associate with ubiquitously expressed AGO subfamily members (VAGIN *et al.* 2006; BRENNECKE *et al.* 2007; HOUWING *et al.* 2007).

Small nucleolar RNAs (snoRNAs) are also small non-coding RNAs (60-300 nt length) (Table 1). Recent discoveries have pointed out a wider regulatory function for these small ncRNAs. They seem to be related with ribosomal RNA (rRNA) folding and stabilization. snoRNAs are normally located within introns of protein-coding genes and are transcribed by RNA polymerase II, although in some cases they can be found within introns of lncRNAs (SMITH AND STEITZ 1997; BORTOLIN AND KISS 1998).

Long noncoding RNAs (lncRNAs) are longer than 200 nt and have been described as potent regulators of gene expression at different levels (Table 1). lncRNAs are also RNAPII transcripts and regulate protein expression by numerous mechanisms (SILVA *et al.* 2003). They participate in the modification of alternative splicing (BARRY *et al.* 2014), depletion of mRNA through decay mechanisms (GONG AND MAQUAT 2011), depletion of endogenous miRNAs (CESANA *et al.* 2011) and also stabilization of mRNAs (FAGHIHI *et al.* 2008). LncRNAs can also play a role in epigenetic regulation such as Xist RNA (17 kb; (MEMILI *et al.* 2001)) and Tsix RNA, antisense Xist RNA (40 kb; (LEE AND LU 1999) involved in X-chromosome inactivation in mammals. Several other lncRNAs are involved in genomic imprinting, such as Air (108 kb; (SLEUTELS AND BARLOW 2002), Kcnq1ot1 (N60 kb; the 3'-end is not fully known; (MANCINI-DINARDO *et al.* 2006)) and H19 (2.3 kb; (CAI AND CULLEN 2007) previously.

Aging

Changes in genome affect its stability, which can promote aging. Aging is known to be influenced by many environmental factors, but over the last years there are many studies where it has been demonstrated that genetic factors can also regulate aging. The molecular mechanism of the cellular aging is conserved across many species. There are many molecular pathways that are related to this process, such as insulin/insulin-like growth factor-1 (IGF-1) signaling pathway (FRIEDMAN AND JOHNSON 1988; KENYON *et al.* 1993) or target of Rapamycin (GUTSCHNER *et al.* 2014) signaling. Analyses of ncRNA functions have provided insights into how aging mechanisms are regulated at different levels (cell, tissue and organism), yielding a better understanding between tumor suppression and the onset of aging-related diseases (SLACK 2013). In this review, will focus on the role of miRNAs and lncRNAs in aging process.

miRNAs and aging

The first miRNAs to be identified, *lin-4* and *let-7*, were described as regulators of developmental timing in the nematode (LEE *et al.* 1993; WIGHTMAN *et al.* 1993; REINHART *et al.* 2000). Since this discovery, by microarray and deep-sequencing analyses many other miRNAs have been discovered in the nematode (LAU *et al.* 2001; REINHART *et al.* 2000). It is known that the expression levels of miRNAs change over time (DE LENCASTRE *et al.* 2010; IBANEZ-VENTOSO *et al.* 2006; KATO *et al.* 2011). However, the correlation between changes in miRNA expression and aging has not been well established.
Specifically *lin-4*, *miR-34, miR-71*, *miR-238* and *miR-246* promote longevity (see below).

The miRNA *lin-4* regulates the protein Lin-14, an essential transcription factor that modulates a variety of signaling pathways controlling developmental timing and lifespan. Animals carrying a deletion mutation of the *lin-4* miRNA display a shorter lifespan, while its overexpression causes a longer lifespan (BOEHM AND SLACK 2005; HRISTOVA *et al.* 2005). The increase in longevity caused by up-regulation of *lin-4* appears to be mediated by the insulin/ IGF signaling pathway.

On the contrary, *let-4* and *miR-239* antagonizes longevity (DE LENCASTRE *et al.* 2010; IBANEZ-VENTOSO *et al.* 2006; KATO *et al.* 2011; CHENG *et al.* 2011). Additionally, a study of *Drosophila* body size showed that *miR-8* (homologous of *miR-200* in humans) regulates insulin pathway being very important for controlling *Drosophila* and human aging (HWANGBO *et al.* 2004; HYUN *et al.* 2009). Other regulators of aging such as *miR-17-92* has also been described in mammals (GRILLARI AND GRILLARI-VOGLAUER 2010).

Currently, thousands of miRNAs have been identified in plants and animals, with over 1400 human miRNAs annotated in the miRBase (http://www.mirbase.org/) (KOZOMARA AND GRIFFITHS-JONES 2011). Measurement of the miRNA levels in blood and its correlation with the age of mice or humans (ZOVOILIS *et al.* 2011), and also as a report of a single miRNA could function as marker for brain aging and neurodegeneration (LI *et al.* 2011).

However, these patterns give the impression to be generally tissue-specific (HOLZENBERGER *et al.* 2003). It should be ideal if the expression profile of these age-associated miRNAs could be used to predict future longevity (PINCUS *et al.* 2011) instead of the conventional biomarkers of longevity (body size, movement rates and accumulation of age pigments).

lncRNAs and aging

Expression of many lncRNAs also changes in the process of aging as global rearrangement of transcriptional regulation follows with aging (GUPTA *et al.* 2014). A few years ago, a potential role of some lncRNAs as regulators of NF-κB pathway (skin aging and rejuvenation) was described (ADLER *et al.* 2007). NF-κB is one transcription factor that controls transcription of DNA and is strongly associated with aging (ADLER *et al.* 2007). The pseudo gene lncRNA, *lethe*, is a negative feedback inhibitor of NF-κB signaling pathway (WANG AND CHANG 2011). The age-associated loss of Lethe expression could be one of the causes for increased NF-κB activity in aging. *Lethe* is induced by proinflammatory cytokines via NF-κB or glucocorticoid receptor agonist, and then *Lethe* is recruited to the NF-κB effector subunit RelA to inhibit RelA from target gene activation (RAPICAVOLI *et al.* 2013).

Furthermore, a number of novel lncRNAs are associated with replicative senescence. Senescence-associated lncRNAs (NA-SAL-RNAs) and pseudogene-encoded lncRNAs (PE-SAL-RNAs) have recently been discovered, which have differential expression during senescence (ABDELMOHSEN *et al.* 2013). Among them, silencing *XLOC_ 025918 and XLOC_ 025931* led to lowered proliferation and increased chance of apoptosis. *MALAT1* is also known to have lower expression level in senescent cells, and silencing *MALAT1* led to an increase in the number of senescent fibroblasts (ABDELMOHSEN *et al.* 2013). All demonstrates that lncRNAs might have anti-ageing effect, but how such lncRNAs regulate gene expression in response to aging and senescence is not known (NIE *et al.* 2012). Although, still much is left to realize the exact role of lncRNAs in aging and related diseases, during the last years a lot of evidences point to an important implication of them in such processes. There are various groups of lncRNAs that directly or indirectly can be involved in the onset or progression of aging. Some of them are differentially expressed and involved in specific mechanisms, such as chromatin or telomere associated, p53 induced or tumor suppressors. Eg, *H19, HOTAIR or ANRIL* are chromatin associated and they regulate development related genes and growth. *TERRA* is an eg of lncRNAs telomere

Table 1. The main classes of non coding RNAs (ncRNAs)

ncRNA	function	species	length (nt)
constitutive ncRNAs			
transfer RNAs (tRNAs)	translation	all	60-100
small nuclear RNAs (sRNAs)	splicing, mRNA processing	eukaryote	60-350
small nucleolar RNAs (snoRNAs)	RNA modification, rRNA processing	eukaryote, archaea	60-300
ribosomal RNAs (rRNAs)	translation	all	120-4700
regulated ncRNAs			
micro RNAs (miRNAs)	transcriptional and translational regulation	all	19-24
small interfering RNAs (siRNAs)	protection against viral infection	eukaryote	21-25
PIWI-interacting RNAs (piRNAs)	genome stabilization	eukaryote	24-30
long noncoding RNAs (lncRNAs)	transcription, splicing, transport regulation	eukaryote	hundreds-thousands

associated, increased levels are associated with telomere shortening, and then cellular senescence and apoptosis. Eg, *PANDA, lincRNA-p21, LINC-ROR* are p53 induced. Their defective expression leads to apoptosis or growth arrest. And defects in the *MEG3, ANRASSF1 or PTENpg1* expression could be implicated in cellular senescence (ANGRAND *et al.* 2015; GRAMMATIKAKIS *et al.* 2014; KANDURI 2016; QUINODOZ AND GUTTMAN 2014).

Conclusions

miRNAs and lncRNAs have appeared as main regulators of chromatin structure, gene expression, epigenetic regulation, RNA processing, protein synthesis, cell signaling and recruitment of various RNAs as well as proteins to DNA/RNA-protein complexes essential for numerous important cellular procedures. Given the impact of aging in our life and in related diseases, there is an important interest in clarifying the molecular mechanism and the regulators of aging in order to intervene therapeutically this process.

As we gain a deeper understanding of the expression and function of ncRNAs, we can anticipate that many of these ncRNAs could have clinical value in diagnosis and therapy. The possibility of their detection in blood or fluids of our body, make these RNAs exceptionally nice-looking as diagnostic and possibly also prognostic biomarkers.

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