ISSN 2079-0570, Advances in Gerontology, 2021, Vol. 11, No. 4, pp. 351–361. © Pleiades Publishing, Ltd., 2021.

Relationship of Peptides and Long Non-Coding RNAs with Aging

R. N. Mustafin*

Bashkir State Medical University, Ufa, 450008 Russia

**e-mail: ruji79@mail.ru*

Received March 8, 2021; revised April 28, 2021; accepted May 11, 2021

Abstract—The paper summarizes data on the existence of evolutionarily fixed species balance of interactions between peptides, RNA, and DNA that provide the stability of the development and functioning of tissues and organs in ontogenesis. Identification of key structures that disturb this balance with aging can become a basis for a specific targeted effect on reversible epigenetic mechanisms of their origin. Non-coding RNAs that, in addition to the function of ribozymes and effectors of RNA interference, are capable of being translated into peptides, which can be the most convenient targets. The effect of the latter on non-coding RNAs and involvement in the same biological processes can become a basis for a complex approach in the development of new geroprotective drugs. It was suggested that peculiarities of the expression of non-coding RNAs typical for a cell type and stage of development reflect transposon activation patterns (programmed at the species level) required for setting of tissue-specific gene networks. This is caused by the formation of non-coding RNAs from transposon transcripts that are regulators of the expression of protein-coding genes in successive cell divisions.

Keywords: long non-coding RNAs, microRNAs, peptides, aging, transposons

DOI: 10.1134/S2079057021040081

INTRODUCTION

Aging is a universal, evolutionary conservative, and genetically controlled biological process characterized by a cumulative decrease in physiological functions and their coordination in the organism after reaching adulthood. Aging is the main risk factor for the occurrence of diseases of cardiovascular, nervous, immune systems, metabolic diseases, and cancer [33]. Genomic instability, telomere depletion, epigenetic changes, loss of proteostasis, stem cell depletion, changes in intercellular connections, and cellular aging are typical molecular traits of aging [22]. Age-related changes occur in the proteome and transcriptome. Due to the creation of different projects such as FANTOM (Functional Annotation of the Mammalian Genome) and ENCODE (Encyclopedia of DNA elements), it became known that approximately 98% of nucleotide sequences (NSs) of mammalian genomes are transcribed into countless multifunctional forms of RNA molecules known as non-coding RNAs (ncRNAs). They are divided into small ncRNAs 20–30 nucleotides in size (they include microRNA, piRNA, siRNA) and long ncRNAs (lncRNAs) consisting of more than 200 nucleotides. At the same time, only 1.5% of the genome is transcribed into exons of protein-coding genes (PCGs). Therefore, most NSs, which is a source of functional ncRNAs, can be considered as potential targets to study the mechanisms of aging. Indeed, in recent years, data have been accumulated on the role of lncRNA in these processes, many of which are evolutionary conservative and specific for primates [33]. LncRNAs have common traits with coding mRNAs (they are transcribed by RNA polymerase II, are exposed to splicing and capping). However, lncRNAs are expressed at a lower level and are involved in different regulatory networks like ribozymes. This occurs due to their ability to fold into complex three-dimensional structures that bind to specific DNA, RNA, and proteins [20].

Aging is associated with a progressive imbalance in the functions of organs, tissues, and individual cells, which leads to a decrease in immunity, cognitive functions, stress resistance, interruption of blood flow, and metabolism. At a molecular level, these processes are caused by interrupting the synthesis of specific lncRNAs (Fig. 1) that modulate the work of the genes at transcriptional, post-transcriptional, and post-translational levels. They can be expressed from intergenic regions (long intergenic noncoding RNA, lincRNA), from the opposite mRNA strand (antisense RNA, asRNA), from rudimentary genes that lost their coding potential (pseudogene-encoded lncRNA), from the introns of annotated genes (long intronic lncRNA), from the promoters of PCG (promoter-associated lncRNA), and splicing machine (circular RNA, circRNA) [22]. Transposable elements (TEs) that serve as the most important sources of ori-

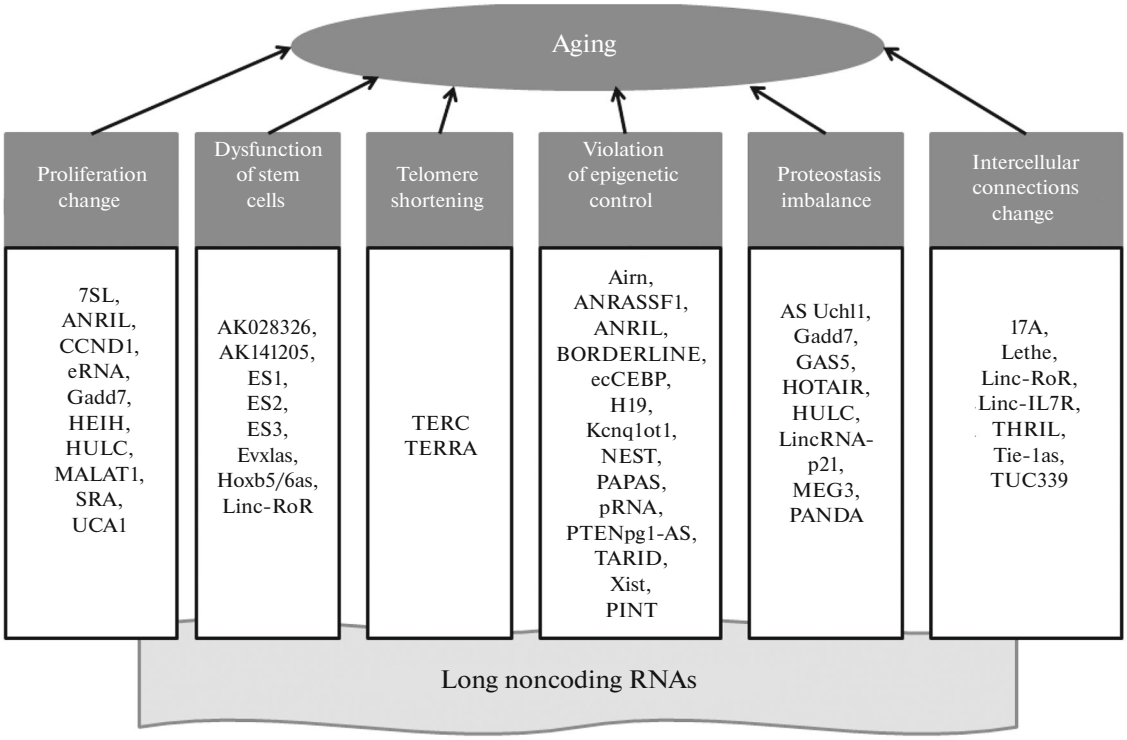

Fig. 1. Role of lncRNA in different mechanisms of aging regulation.

gin and evolution of lncRNA are characterized by a similar localization. Back in 2012 based on the analysis of GENCODE data and RNA sequencing, it was demonstrated that 41% of all lncRNA nucleotides originated from TEs. Most (83%) of all known lncRNAs contain at least one TE fragment [29].

TEs are genome regions that can move to other loci. They are divided into two classes: I, retroelements (REs) that are reproduced by copying and pasting using a reverse transcriptase and intermediate RNA molecules; II, DNA-TEs moving through a cutting and pasting mechanism using a transposase. REs are divided into long terminal repeating (LTR)-containing and non-LTR REs. The latter include long interspersed nuclear elements (LINEs), which are most common in the human genome [14]. The products of LINE transcription can directly function as lncRNA affecting the expression of specific genes and chromatin regions [25]. Human LTR-containing REs include HERVH endogenous retroviruses that can serve as lncRNA genes required to maintain the identity of embryonic stem cells [41].

LncRNAs are able to regulate the chromatin state and methylation by recruiting remodeling factors in *cis* and in *trans*; act as guides for targeting specific genomic loci; mediate antisense interference for coding mRNAs; act as a carcass for the interaction of proteins with transcription factors and chromatin modifiers; and function as a bait (sponge) to inactivate microRNA [20]. At a post-transcriptional level, lncRNA can pair with mRNA and regulate their translation and stability, as well as manage splicing and translation by interference with RNA-binding proteins. Some lncRNAs directly control protein metabolism, facilitating ubiquitination [22]. Like proteins, lncRNAs have a modular organization due to individual domains that in combination determine the functions of these molecules. There are at least two separate mechanisms of realization of the effects of lncRNA domains: (1) organization of specific secondary structure providing the interaction with protein partners: (2) hybridization with other nucleic acids based on complementarity of NSs [27]. In addition to transcription by RNA polymerase II, formation of 5'-cap, and polyadenylation, lncRNAs are similar to PCGs due to their regulation by transcription factors p53, Oct, and Nanog. LncRNA genes are also characterized by specific transcriptional chromatin marks: trimethylation of H3K4 and H3K36, acetylation of H3K9, methylation of CpG [33].

According to NONCODEv4 database (http:www.noncode.org) [71], many lncRNAs in human genome are evolutionarily new; out of them, approximately 1/3 are primate-specific [9]. In 2020, 96308 human lncRNA genes were annotated in NONCODEv4, which significantly exceeds the number of PCGs. The role of lncRNAs in aging is caused by their involvement in the control of gene expression during cell differentiation. The highest activity of lncRNAs was detected in tissues, in which a maximal

diversity of cell phenotypes is required to provide organ functioning. These properties are possessed by the brain for the work of which a huge number of neurons differing in properties in its specific structures are required [48]. In adult mice, 849 out of 1328 known ncRNAs are expressed in the brain. Many of these molecules are associated with specific neuroanatomical areas and cell types. The comparison of lncRNAs expression profiled and PCGs associated with them demonstrated the presence of relationships between them according to cell type [47]. A decrease in cognitive function and neurogenesis, increased risk of neurodegenerative diseases are typical changes of human brain with aging. These peculiarities are caused by imbalance of epigenetic regulation and transcription, as well as regular changes in coding and non-coding regions of the genome. A key role in these processes is played by lncRNAs that, as previously suggested, have almost no ability to encode the protein [56]. However, according to resent studies, the possibility of lncRNA translation with the formation of peptides [6, 51, 70], that can be promising objects for the development of geroprotective preparations, was proven in several works. It is necessary to take into account tissue-specific peculiarities of lncRNA transcription associated with the effect of programmed activations of TEs that are a kind of drivers for regulation of lncRNAs and epigenetic factors [1]. In this regard, the consideration of the peculiarities of lncRNA expression depending on the tissue and stage of development, its changes with age is of interest to determine possible ways of influencing the molecular mechanisms of aging.

TISSUE SPECIFICITY OF LONG NON-CODING RNA AND TRANSPOSONS

Genome-wide association studies (GWASs) demonstrated that human lncRNAs are characterized by greater uniqueness of expression depending on the cell type, space, and time as compared with PCGs. This indicates the role of lncRNAs as key regulators of cell differentiation [29]. Together with sense mRNAs, antisense asRNAs (that overlap coding mRNAs of genes) are detected in the area of synapses. When located close to their sense mRNAs, they hybridize and form duplexes. The stability of encoded mRNAs and the levels of their protein products, including involvement in the work of neurons (BDNF, GDNF, EPHB2, KCNA2), are regulated in this way. A change in the expression with aging is observed for some asRNAs, which can play a role in age-related neurodegeneration. In mammals, more than a half of all genes have non-coding asRNAs that are involved in billions of different processes from epigenetic regulation of silencing to stabilization and translation of coding mRNAs [56]. According to the transcription sites of target genes, asRNAs act in *cis* or in *trans* for the regulation of different biological processes, such as genomic imprinting, X chromosome inactivation, alternative splicing, and post-transcriptional RNAi. The association of a number of asRNAs with aging is proven: LSAMP-AS1-001 is antisense for mRNAs associated with the limbic system of membrane protein LSAMP; VCAN-AS1-001, for mRNAs of extracellular matrix proteoglycan (versican); OSTN-AS1-001, for mRNAs of secretory protein osteocrine; and RP11-346A9.1, for mRNAs of metallopeptidase [33]. Antisense ANRIL lncRNA in the INK4 locus regulates CDKN2A/B oncosuppressor; lncRNA Sarrah (SCOT1-antisense RNA regulated during aging in the heart) causes apoptosis and controls heart contractility during aging [66]. Sirt1 AS, which plays a role in progressing organ fibrosis, is an antisense lncRNA for Sirt1 (silent information regulator 1), sirtuin, regulating the proliferation and differentiation of myoblasts [58]. Sirt1 is NAD+-dependent lysine deacetylase activated in response to aging, metabolic changes, and different cell stresses. The activation of Sirt1 using resveratrol prolongs the life of yeasts by 70%. lncRNA Sirt1-AS binds and completely overlaps with 3'-UTR mRNA Sirt1 and increases its stability due to the formation of an lncRNA–mRNA duplex [40].

The prospects of using lncRNA for a possible correction of aging is associated with the fact that despite the abundance of different lncRNAs in tissues and organs, even one specific RNA molecule can have a pronounced effect on their development. Genome-wide transcriptome analysis of normal diploid fibroblasts demonstrated that lncRNA MALAT1 modulates the expression of cell cycle genes and is required for the transition of the G1 to S phase of mitosis. A depletion of MALAT1 leads to the activation of p53 and its target genes. In the cells devoid of MALAT1, a reduced expression of oncogenic transcription factor B-MYB required for the transition of the G2 to M phase is manifested [65]. lncRNA UCA1 negatively regulates the protein complex CAPERα/TBX3, although it contributes to carcinogenesis in transformed cancer cells. The suppression of MALAT1 in cervical cancer cells causes cell cycle arrest, an increase in cellular aging, and a decrease in tumor size by affecting the B-MYB transcription factor. lncRNA PANDA interacts with PRC and scaffold-attachment factor A (SAFA), suppressing gene transcription and contributing to aging. HOTAIR interacts with repressor complex PRC2 causing the suppression of HOXD locus, contributing to aging [5].

The tissue specificity of lncRNAs is associated with their role in the regulation of the development and growth of the organism, apoptosis, reprograming of differentiating cells, and maintenance of stem cells. Many lncRNAs are localized in the nucleus and regulate the gene expression as enhancer RNA (for example, Evf-2 stimulates the transcription), modify the chromatin by recruiting DNA methyltransferases and histone modifiers (for example, XIST, HOTAIR), and regulate RNA transport by their editing (ALU-RNA). Some lncRNAs are transported to the cytoplasm and

function as translation modulators (UCH1-AS1, ubiquitin carboxy-terminal hydrolase L1 antisense RNA1), maintain mRNA stability by isolating microRNA (lincMD1), or prevent degradation when mating with 3'UTR (1/2-sbsRNA, lincRNA-p21), are used as precursors of small ncRNAs (MALAT1) [33]. In 2011, when studying 8000 intergenic lincRNAs in 24 tissues, M.N. Cabili at el., demonstrated that the expression of these lincRNAs has a remarkable tissue specificity. At the same time, co-expression with neighboring PCGs is peculiar for them. The additional subgroup of transcripts, which has high evolutionary conservatism and is able to include short open reading frames (short ORF, sORF) and translate into peptides, was isolated [12]. These data can reflect the abilities of genomes to co-opt TE sequences depending on their significance for the adaptation and survival of the organisms. That is, if germinative insertions in the evolution contribute to the best adaptability of individuals and their preservation during selection, the mechanisms of conservation of these sequences in the genome are activated; as a result, lncRNA genes are formed from TEs. This assumption can be justified by a similar tissue specificity of TEs. However, TEs themselves have a high mobility and ability to cause "harmful" mutations while preserving them in the genome. In this regard, those individuals are preserved in the course of evolution, in which genome TEs useful for adaptation either are inactivated and used as lncRNA genes or are a part of and under the control of epigenetic networks of gene control. Like lncRNA, human transposons are also characterized by tissue-specific peculiarities of expression [67]. Moreover, activated TEs are drivers for the regulation of expression of PCGs in different tissues [55], which can explain similar peculiarities for lncRNAs, since TEs are the most important sources of the emergence of lncRNAs in evolution [27, 29].

EFFECT OF LONG NON-CODING RNAs ON AGING MECHANISMS

LncRNAs taking a specific part in organism aging were identified. They are designated as senescence-associated lncRNAs (SAL-RNAs). When comparing the expression of lncRNAs in proliferating "young" fibroblasts with those in "old" cells, it was demonstrated that a decrease in the levels of SAL-RNA1 (XLOC_023166) enhances the manifestation of phenotypic traits of aging, including increased sizes, positive β-galactosidase activity, and increased level of p53 [4]. In the experiment on cell cultures of human fibroblasts, the involvement of such lncRNAs in cellular aging as MIAT, XIST, TUG1, MALAT1, RP11-255A11.21, and RP11-394.O4.4 (that are also involved in epigenetic regulation throughout ontogenesis) was detected [33]. This supports the fact that the same lncRNAs are involved in the mechanism of aging and organism development. Multiple studies demonstrated the role of lncRNAs in a change in different aging mechanisms, including epigenetic and transcription factors and cell differentiation control systems (Table 1) [22]. Despite a pronounced evolutionary variability and species specificity, there are families of evolutionary conservative lncRNAs designated as Transcribed ultraconservative elements (T-UCE) the sequences of which are identical for human, mouse, and rat genomes (for example, Evf-1/2, Dlxlas, T-UC.283+, T-UCstem1, T-UC.77, T-UC.138, T-UC.189, T-UC.338, T-UC.376, T-UC.377, T-UC.359, AK141205, DIGIT, Evx1as, Meg3, Meteor, Neat1, Pnky, TERRA, and TUNA). They play a significant role in the control of stem cell differentiation in embryogenesis. This process can be also affected by less conservative lncRNAs, such as AK028326, Braveheart, GAS5, Hotair, LincPRESS1, LincRNA1592-1552, Lin-RoR, and Oct4P4 [20].

The involvement of lncRNAs BORDERLINE, PINT, ANRASSF1, ANRIL, NeST, and Kcnq1ot1 in histone modification; TARID, PTENpg1-AS, PAPAS, pRNA, ecCEBP, Airn, Kcnq1ot1, H19, and Xist in DNA methylation; HULC, 7SL, and MEG3 in autophagy; Gadd7, PANDA, GAS5, and 7SL in intracellular protein distribution; and HOTAIR, lncRNA-p21, and AS Uchl1 in protein synthesis and degradation was demonstrated. In addition, the involvement of lncRNAs in the regulation of stem cell transcription factors: AK141205, AK028326, ES1, ES2, ES3, linc-RoR, Evx1as, and Hoxb5/6as; in cell cycle control: MEG3, 7SL, H19, UCA1, eRNAs, Gadd7, HEIH, HULC, NcRNACCND1, ANRIL, MALAT1, and SRA; extracellular signaling pathways through exosomes: Linc-ROR, Tie-1as, TUC339, CCND1-ncRNA, TUG1, GAS5, lincRNA-p21, HOTAIR, and MALAT1 was described [22]. The role of lncRNAs in aging was determined in different organisms. For example, the expression patterns of 5299 different lncRNAs were analyzed in an experiment on zebrafish, and their relationship with changes in H3K9me3 histone trimethylation with aging was detected. It was demonstrated that not only age-related, but also daily changes of H3K9me3 in the genome coincide with the peculiarities of lncRNA transcription [54]. It is interesting that lncRNAs associated with transcription factors that have a global regulatory character on gene expression are involved in the regulation of aging. p53-associated long ncRNAs are an example: PANDA, PINT, TUG1, LincRNA-p21, 7SL, and LincROR. LncRNA affecting the chromatin modification play an important role in aging. They include H19 (expressed at a high level in embryogenesis, functions as a precursor for a number of microRNAs involved in negative regulation of cell growth and proliferation), Kcnq1ot1 (in embryogenesis, regulates gene imprinting by recruiting the chromatin remodeling complex from specific H3K9- and H3K27-histone methyltransferases, repression complex polycomb), ANRIL (recruits the repression complex polycomb PRC1 and

Table 1. Effect of long ncRNA on aging mechanisms

Variable factor	Names of long non-coding RNA
Histone modifications	BORDERLINE, PINT, ANRASSF1, ANRIL, NeST, Kcnq1ot1
DNA methylation	TARID, PTENpg1-AS, PAPAS, pRNA, ecCEBP, Airn, Kcnq1ot1, H19, Xist
Heterochromatin	H19, Kcnq1ot1, ANRIL, Air, ecCEBP, pRNA
Cell cycle control	MEG3, 7SL, H19, UCA1, eRNAs, Gadd7, HEIH, HULC, NcRNACCND1, ANRIL, MALAT1, SRA
Protein synthesis and degradation	HOTAIR, LncRNA-p21, AS Uchl1
Distribution of proteins within the cell	Gadd7, PANDA, GAS5, 7SL
Autophagia	HULC, 7SL, MEG3
Regulation of stem cell transcription factors	AK141205, AK028326, ES1, ES2, ES3, linc-RoR, Evx1as, Hoxb5/6as
Intracellular signaling pathways of the exosome	Linc-ROR, Tie-1as, TUC339, CCND1-ncRNA, TUG1, GAS5, LincRNA-p21, HOTAIR, MALAT1
P53 transcription factor	PANDA, PINT, TUG1, LincRNA-p21, 7SL, LincROR
Stem cell differentiation	Evf-1/2, Dlxlas, T-UC.283+, T-UCstem1, T-UC, AK141205, DIGIT, Evx1as, Meg3, Meteor, Neat1, Pnky, TERRA, TUNA

PRC2), Air (antisense RNA for Igf2r, regulates chromatin-mediated silencing of parental alleles by recruiting histone methyltransferase EHMT2), ecCEBP (recruits DNMT1), pRNA (highly conservative promoter-associated lncRNAs involved in silencing of repetitive transcription units of rRNAs by the formation of heterochromatin in the promoter region of rRNAs) [33].

ROLE OF LONG NON-CODING RNA IN DEVELOPMENT AND AGING OF THE BRAIN

LncRNAs are characterized by a pronounced expression in the brain, where they play a functional role in neuroplasticity, cognitive processes, and stem cell differentiation. It is assumed that the loss of ability to neurogenesis is one of the reasons of aging [56]. In the experimental studies on mice and cell cultures of the brain, it was demonstrated that specific lncRNAs serve as "switches" of gene expression for differentiation of neuronal stem cells to the precursors of oligodendrocytes. Data obtained indicate the role of lncRNAs as regulators of differentiation [17]. It was proven that specific lncRNAs regulate neurogenesis. For example, it was demonstrated that lncRNA rhabdomyosarcoma 2-associated transcript (RMST, the expression of which is enhanced during the differentiation of neurons in the human brain) is indispensable for neurogenesis. RMST physically interacts with SOX2, contributing to its binding to the promoter region of neurogenic transcription factors [53]. LncRNAs play a key role in managing the transition from one stage of differentiation of neuronal stem cells to another, as well as in regulating the amount and type of cells in each of the stages. For example, lncRNA Six3os reduced in the stem cells of subventricular zone in adult mice leads to a twofold decrease in the number of cells positive for neuronal Tuj1 marker and to an increase in the number of cells positive for GFAP (a marker activated by neuronal stem cells). With Dlx1as knockdown, the expression of transcription factors Dlx1/2 decreases, the number of Tuj1-positive neuroblasts decreases 3 times, while GFAP-positive is increased by 60%. The Pnky reduction causes an increase in the formation of neurons by several times [56].

In the experiments, it was demonstrated that 849 out of 1328 known lncRNAs are expressed in the brain in mice. They are associated with specific neuroanatomical regions, cell type, and even subcellular structures. These lncRNAs are transcribed from intergenic, intronic, and imprinted loci, as well as together with PCGs of the nervous system or as their antisense transcripts [47]. There is no doubt that the study of lncRNAs involved in the development of the brain could be a key to elucidating their role in aging. It was demonstrated that specific lncRNAs that are expressed in the mammalian hippocampus in embryogenesis [11] are also determined in an adult in the subventricular zone of neurogenesis [9]. Specific lncRNAs are transported to neuronal dendrites, where they function as mediators for a translational control of local protein synthesis in synapses. For example, BC1 inhibits the formation of preinitiator complex 48S, that is, recruiting of small ribosomal subunits to mRNA. In addition, BC1 interacts with ATP-dependent RNA helicase eIF4A and poly(A)-binding protein in synaptodendritic microdomains [68], thus affecting long-term synaptic plasticity. Since disorders of synaptic plasticity plays a role in Alzheimer's disease, the expression of BC1 was studied with this pathology. A signif-

icant change in the levels of primate-specific BC1 (BC200) in the brain of patients as compared with healthy individuals of the same age was found. In addition, the levels of BC200 are significantly decreased in cortex of the human brain (more than 60% for the period 49–86 years) with normal aging [50].

The role of asRNA in pathological protein aggregation in aging-associated neurodegenerative diseases was detected. For example, they contribute to the aggregation of amyloid beta sheets by controlling the expression and splicing of proteins with Alzheimer's disease [56]. The role of specific lncRNAs in aging of the brain was proven in experiments on rats. LincRNA called LINC-RBE (rat brain expressed), containing simple repeats and SINE, was described. The levels of LINC-RBE differed significantly depending on age and specific neuroanatomical areas, cell type, and even subcellular structures [32]. A significant increase in the expression of some lncRNAs, such as NEAT1, MALAT1, TUG1, and GOMAFU (that are associated with embryonic neurogenesis), was also detected in humans with aging in the subventricular zone [9]. An imbalance of TE activity with age can be a possible prime cause of aging-associated changes in the regulation of lncRNA [10, 14, 16], because many lncRNAs are formed by processing of RNA transposons, while REs can serve directly as lncRNA genes [25, 29, 41]. Data on the relationship of lncRNAs with telomeres, that as well as lncRNAs [27] and telomerase [31] originated from TEs in evolution, can be a confirmation of this assumption. Moreover, the role of LINE1 in the maintenance of telomeres in ontogenesis was proven [49].

In eukaryotes, each cell is divided a certain number of times, after which it ages and undergoes apoptosis. This is accompanied by shortening of telomeres at the ends of chromosomes (fragments of double-stranded repeating NSs (5'-TTAGGG-3'/5'-CCCTAA-3') ending in a single-stranded G-rich lip). The telomeres protect the chromosome ends from DNA damage, degradation, recombination, and fusion with other chromosomes. The loss of their function due to mutations or inhibition of telomerase activity causes a chromosome instability and premature cellular aging [33]. The length of telomeres is regulated by a telomerase ribonucleoprotein complex containing TERT protein, long ncRNA TERRA (Telomeric Repeat-containing RNA), and TERC (Telomerase RNA Component) [22]. According to numerous studies, aging and its associated diseases are associated with dysfunction of telomeres. The activity of telomerase in neuronal stem cells (NSCs) isolated from the hippocampus is typical in the brain of adult mice. The expression of telomerase reverse transcriptase (TERT) decreases with aging in these areas, as a result of which telomeres are shortened, and neurogenesis is impaired. Similar processes are also observed in other tissues with aging. It was proven that lncRNAs play a key role in stem cell telomere dynamics. For example, TERC is a matrix for the synthesis of new telomere repeats, as well as act as a scaffold combining protein subunit of telomerase. TERRA is transcribed from subtelomeric regions of the chromosomes and pairs with complementary nucleotides at the ends of the chromosomes, forming hybrid RNA–DNA structures that regulate the telomere length. As a human ages, TERRA levels are inversely correlated with telomere length [56]. The activity of telomerase in the brain of adult mice is specific for NSCs isolated from the subventricular zone and hippocampus. It is interesting that the suppression of total subtelomeric transcription due to a temporary activation of mitochondrial reactive oxygen species (as it was demonstrated in yeasts) prolongs the life span [63]. That is, the effect of free radicals regarding telomeres can be a stimulus for slowing down aging, but not for its induction. Correspondingly, there must be other reasons for the shortening of NSC telomere length with aging.

The expression of TERT decreases with aging in the subventricular zone of mice, leading to shortening of telomeres and severe impairment of neurogenesis. In most somatic tissues, telomeric DNA shortens progressively with each round of DNA replication with a rate 50–200 bp per each cell division [7]. Telomere shortening and dysfunction of telomere-binding proteins leads to genomic instability and fusion of the ends of chromosomes. The proliferation rate in NSCs of the adult brain in mice deficient for telomerase is gradually decreasing. However, similar changes are also observed in NSCs with normal telomerase function, which indicates the presence of other mechanisms for maintaining proliferative potential of SCs [18]. TEs, the relationship of which with telomeres and telomerase was proven in a number of studies, are the most probable candidates. Indeed, telomerase itself came from retroelements in evolution [35], while the loss of telomerase in Drosophila was successfully compensated by the function of HeT-A, TART, and TAHRE retroelements [15]. A direct influence of REs in maintaining the functioning of telomeres was proven [6]. There is an epigenetic relationship of telomerase and transposons. For example, mRNA products of both TERT genes and reverse transcriptase of LINE1 elements are targets of the same miR-128 microRNA [23]. miR-340 microRNA originated from the TcMar-Mariner DNA transposon [37] causes lengthening of telomeres by a targeting effect on the POT1 (protection of telomere 1) protein [39]. In the *Bombyx mori* silkworm, SART1Bm REs have a targeted effect on TTAGG repeats and is involved in maintaining the telomere length with normal development. The experiments demonstrated that SART1Bm can move to telomeric repeats of other species, including human TTAGGG [52]. In humans, the role of LINE1 in maintaining the telomere length in tumor cells was detected [7, 8]. A dysfunction of TEs is typical both for carcinogenesis [59] and aging [10, 14, 46]. Correspondingly, shortening of telomere length in

NSCs with aging can only reflect a global imbalance in TE regulation. At the same time, the alternative telomeres lengthening using LINE1 [8] can be used in the future to treat the diseases caused by shortening of telomeres [61].

A shortening of telomeres in NSCs during aging can also be associated with the fact that telomerase activity is insufficient to preserve completely the telomere length in the cells replicating throughout life. Telomere shortening to a critical level leads to the activation of p53, which causes limitation of proliferation of NSCs and/or their apoptosis [19]. It is interesting that p53 also has a regulatory effect on TEs. Particularly, 1509 different LTRs in the human genome are p53 binding sites [69], while binding of 5'UTR LINE1 elements with p53 protein leads to their repression due to histone modification [64]. That is, direct mutual regulation of TEs → telomeres → p53 → TEs is observed with aging, since deregulation of TEs with age [1] leads to shortening of telomeres that activate p53, while the latter causes repression of transposons. In this respect, p53 protein acts as a stabilizer preventing the development of genomic instability caused by dysfunction of both telomeres and transposons. It is possible that such relationship has a universal character and was developed evolutionarily as an adaptive process required to maintain genome stability. However, this mechanism is not perfect, since the repression of necessary to maintain pluripotency LTR-RE [21] leads to a depletion of proliferative potential of NSCs and inevitable aging under the influence of p53, which also represses TERT. In turn, TERT controls the activity of p53 leading to a progressive aging in a system of TEs → telomeres → p53 → TEs [43].

RELATIONSHIP OF LONG NON-CODING RNA WITH TRANSPOSONS AND PEPTIDES

The peptides are classified by size, 3D structure, covalent pairing pattern, their biological sources, and methods of biosynthesis (gene-encoded ribosomal and not encoded by genes that are non-ribosomal). The peptides with classical ORF are expressed on ribosomes by larger precursors with subsequent processing to shorter peptides using posttranslational modifiers. In addition, in mature mRNA, ribosomes can select different translation initiation sites or alternative start codons instead of classical ATG. The peptides encoded by the reading frame upstream of the gene (upstream ORF), short ORF (sORF), and micro ORF (miORF) are distinguished [62]. At present, the peptide drugs developed by V.H. Khavinson [3] are successfully used in gerontology and geriatrics. The experience gained can become a basis for studying the possibility of using the products of lncRNA translation having a wide range of action. In future, this approach would make it possible to develop highly efficient drugs for prolonging human life. It caused by the relationship of lncRNAs with transposons affecting a global regulatory role on the functioning of the human genome with aging [1].

Traditional approaches for classification of RNA with a protein-coding potential are based on the existence of long ORFs. In this regard, many transcripts were annotated as ncRNA due to the absence of ORFs longer than 100 codons. However, there are sORFs with a length less than 100 triplets capable of binding to ribosomes. lncRNAs are characterized by the presence of both sORFs and other ORFs required for their translation. For example, approximately 10% of sORFs play a functional role in *Arabidopsis thaliana* [38]. Profiling of ribosomes in mammalian genomes using a deep sequencing of ribosome-protected mRNA fragments with a digital data processing method allowed us to determine that most lncRNAs contain regions with a high potential for translation similar to those for PCGs [26]. In *Drosophila*, short peptides called Pri with a length from 11 to 32 amino acids, encoded by lncRNA, were detected. Pri control epidermal differentiation by modifying the Svb transcription factor (convert from a repressor to an activator by a terminal shortening). It was demonstrated that during embryogenesis of *Drosophila*, Pri provide a strict time control of the transcriptional program of epidermal morphogenesis [30]. The genome of *Drosophila* contains approximately 600000 sORFs, out of which at least 4561 are functional [34].

The possibility of lncRNA translation for regulating the genome function provides additional adaptive capabilities due to a comprehensive control of gene expression. The translation of SgrS ncRNA in *Escherichia coli* with the formation of SgrT peptide can be given as the simplest example. Under conditions of a glucose–phosphate stress, non-coding SgrS RNA due to nucleotide pairing with mRNA prevents the translation of PtsG and ManXYZ glucose transporters. At the same time, the SgrT peptide directly interacts with PtsG protein and inhibits its function [62]. In mammals, lncRNA SRA (steroid receptor RNA activator) acts as a transcriptional coactivator of steroid hormone receptor and is involved in differentiation of muscle cells. Several splicing variants of SRA gene transcripts, some of which include candidate open reading frames and two potential start codons for SRAP proteins, were detected. These polypeptides show biological activity as a modulator of SRA-dependent regulation of transcription. That is, SRA and SRAP exhibit a bilateral genetic system, where RNA and protein products of the same gene play a specific and sometimes overlapping role in cell biology [16].

Using the DMDA-PatA translation inhibitor for accurate detection of translated ORFs even for rare transcripts, it was demonstrated that from 1/3 to 2/3 of lncRNAs in embryonic stem cells of mice are translated [57]. Many examples in animals and plants about the significance of peptides formed during lncRNA translation in the organism development were

described [60]. For example, the lncRNA pncr003:2*L* gene was found, which encodes two peptides with a length 28 and 29 amino acids that regulate the transport of calcium ions through the sarcoplasmic reticulum. They were conservative for over 550 million years in several animal species (from flies to humans). In humans, these lncRNAs were involved in heart pathology [44]. Later, a conservative micropeptide out of 46 amino acids called MLN (myoregulin), encoded by muscle-specific lncRNA, was discovered. This peptide has structural and functional similarity to sarcolipin and phospholamban that inhibit the absorption of calcium ions through the membrane of the sarcoplasmic reticulum [6]. In 2016, B.R. Nelson et al. described muscle-specific lncRNA translated into a peptide of 34 amino acids called DWORFs (dwarf open reading frame). Localized in the membrane of sarcoplasmic reticulum, DWORF displaces myoregulin, sarcolipin, and phospholamban, thus enhancing the activity of SERCA (sarco-endoplasmic reticulum Ca2+ adenosine triphosphatase) [51]. In 2017, A. Matsumoto et al., detected encoded by lncRNA, LINC00961 functional polypeptide, which is conserved from mouse to human and is localized in lysosomes, where it interacts with lysosomal v-ATPase for a negative regulation of mTORC1 activation. A tissue specific regulation of mTORC1 expression was a characteristic feature of this lncRNA [45]. Using full-length translational mRNA sequencing and human ribosome profiling, it was found that more than 3330 lncRNAs bind to the ribosomes with active translational elongation. 308 new proteins encoded by lncRNA were described [42].

It is most likely that the role of lncRNA in the genome regulation and formation of peptides reflects evolutionary function of TEs to ensure the adaptive properties of the organisms. This is reflected in species-specific peculiarities of life expectancy, which is associated with the composition and distribution of TEs in genomes. The clarification of key TEs affecting the peculiarities of aging of different species can become a basis for the search for peptides with a potential geroprotective role. Indeed, in addition to the involvement in the formation of mature lncRNA transcripts, transposons form for their genes promoters, donor and acceptor splicing, and polyadenylation sites [27]. The peculiarities of TE distribution in genomes are reflected on interspecific differences of the composition of TEs in the genes of their lncRNA [28]. In the human genome, both LINE1 and LTR-RE (from which thousands of lncRNAs originated) are the sources of lncRNA. In addition, non-autonomous REs Alu are actively incorporated into lncRNA genes forming the structures interacting with PCG mRNA due to short imperfect nucleotide pairings [24]. It was proven that the transcripts of LTR-RE [41] and LINE1 [25] themselves function as lncRNA. At the same time, they interact with specific chromatin regions and regulate gene expression at different stages of ontogenesis, beginning from a bicellular stage [25]. It is most likely that all lncRNAs during evolution originated from TEs, which can explain the content of TE sequences in most genes [27, 28]. A change in their structure and difference from initial TE genes (their sources) can be associated with the use of lncRNAs for the needs of hosts and accumulation of adaptive mutations most suitable for the regulation of genome function. However, the preservation of TE sequences in the structure of their genes allows lncRNA to participate in interactions with regulatory networks formed during evolution using TEs. The studies on the search of lncRNA as targets for the effect on aging processes are already carried out. For example, several aging-associated lncRNAs was detected during the comparative analysis of the levels of lncRNA expression in young and old human fibroblasts. Among them, SAL-RNA1 (XLOC_023166) was detected, low concentrations of which increased the appearance of phenotypic traits of aging such as increased sizes, positive β-galactosidase activity, and increased p53 levels [4].

The involvement of lncRNAs and products of their translation in common biological processes opens up prospects for a search for new peptides in gerontology for a more successful effect on aging. An innovative approach, which consists in the analysis of known lncRNAs involved in the mechanisms of a change in life span, is possible. Their products of translation can have a large regulatory potential both due to the effect on the same molecular targets as lncRNA and by regulating the expression of lncRNA genes. Such mechanisms were described for the peptides formed from pri-microRNA [36]. Their interaction with double stranded DNA can be a possible mechanism of this effect [2].

CONCLUSIONS

Long ncRNAs play a key role in human organism aging. This is associated with their tissue-specific effect on epigenetic control of PCG expression at different stages of ontogenesis. The peptides formed due to lncRNA translation are able to affect both PCG and production of lncRNA. In this regard, the study of specific peptides formed from ncRNA for the development of ways to prolong life and therapy of age-associated pathology can become a promising direction in gerontology. The investigation of changes in TE activity that are sources of lncRNA both in evolution and in ontogenesis is important in this direction. It is most likely that species-specific set and distribution of TEs in the genome serve as a root cause of changes in lncRNA expression in each cell division, which is reflected on the genome functioning in ontogenesis. The level of lncRNA transcription is lower than mRNA of protein-coding genes. At the same time, lncRNAs are translated to functional peptides and even protein molecules involved in biological processes united with their transcripts. It can be assumed

that it reflects evolutionary conservative property of the organisms to form a large number of potentially new functional RNA molecules and products of their translation to adapt to changing environmental conditions. Therefore, pronounced changes in lncRNA expression with aging can reflect the adaptive processes in the organism associated with an imbalance on the genome functioning. Determination of the most successful of such adaptive processes can become a basis for the selection of specific lncRNA translation products to slow down the aging processes.

COMPLIANCE WITH ETHICAL STANDARDS

The author declares that he has no conflicts of interest. This article does not contain any studies involving animals or human participants performed by the author.

REFERENCES

1. Mustafin, R.N. and Khusnutdinova, E.K., The interaction of transposons with epigenetic factors in aging, *Usp. Gerontol.*, 2017, vol. 30, no. 4, pp. 516–528.
2. Khavinson, V.Kh., Solovyov, A.Yu., and Shataeva, L.K., Molecular mechanism of interaction between oligopeptides and double-stranded DNA, *Bull. Exp. Biol. Med.*, 2006, vol. 141, no. 4, pp. 457–461.
3. Khavinson, V.Kh., *Peptidnaya regulyatsiya stareniya* (Peptide Regulation of Aging), St. Petersburg: Nauka, 2009.
4. Abdolmohsen, K., Panda, A., Kang, M.J., et al., Senescence-associated lncRNAs: senescence-associated long noncoding RNAs, *Aging Cell,* 2013, vol. 12, pp. 890–900.
5. Abdelmohsen, K. and Gorospe, M., Noncoding RNA control of cellular senescence, *Wiley Interdiscip. Rev.: RNA*, 2015, vol. 6, no. 6, pp. 615–629.
6. Anderson, D.M., Anderson, K.M., Chang, C.L., et al., A micropeptide encoded by a putative long noncoding RNA regulates muscle performance, *Cell*, 2015, vol. 160, pp. 595–606.
7. Aschacher T., Wolf B., Enzmann F., et al., LINE-1 induces hTERT and ensures telomere maintenance in tumour cell lines, *Oncogene*, 2016, vol. 35, pp. 94–104.
8. Aschacher, T., Wolf, B., Aschacher, O., et al., Long interspersed element-1 ribonucleoprotein particles protect telomeric ends in alternative lengthening of telomeres dependent cells, *Neoplasia,* 2020, vol. 22, pp. 61–75.
9. Barry, G., Guennewig, B., Fung, S., et al., Long noncoding RNA expression during aging in the human subependymal zone, *Front. Neurol.*, 2015, vol. 6, p. 45.
10. Bravo, J.I., Nozownik, S., Danthi, P.S., and Benayoun, B.A., Transposable elements, circular RNAs and mitochondrial transcription in age-related genomic regulation, *Development,* 2020, vol. 147, pp. 175786.
11. Briggs, J.A., Wolvetang, E.J., Mattick, J.S., et al., Mechanisms of long non-coding RNAs in mammalian nervous system development, plasticity, disease, and evolution, *Neuron,* 2015, vol. 88, pp. 861–877.
12. Cabili, M.N., Trapnell, C., Goff, L., et al., Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses, *Genes Dev.,* 2011, vol. 25, no. 18, pp. 1915–1927.
13. Cao, Q., Wu, J., Wang, X., and Song, C., Noncoding RNAs in vascular aging, *Oxid. Med. Cell. Longevity*, 2020, vol. 2020, art. ID 7914957.
14. Cardelli, M., The epigenetic alteration of endogenous retroelements in aging, *Mech. Ageing Dev.*, 2018, vol. 174, pp. 30–46.
15. Casacuberta, E., Drosophila: retrotransposons making up telomeres, *Viruses,* 2017, vol. 9, p. 192.
16. Cooper, C., Vincett, D., Yan, Y., et al., Steroid receptor RNA activator bi-faceted genetic system: heads or tails, *Biochimie,* 2011, vol. 93, pp. 1973–1980.
17. Dong, X., Chen, K., Cuevas-Diaz Duran, R., et al., Comprehensive identification of long non-coding RNAs in purified cell types from the brain reveals functional lncRNA in OPC fate determination, *PLoS Genet.,* 2015, vol. 11, pp. 1–26.
18. Ferron, S.R., Mira, H., Franco, S., et al., Telomere shortening and chromosomal instability abrogates proliferation of adult but not embryonic neural stem cells, *Development,* 2004, vol. 131, pp. 4059–4070.
19. Ferron, S.R., Marques-Torrejon, M.A., Mira, H., et al., Telomere shortening in neural stem cells disrupts neuronal differentiation and neurogenesis, *J. Neurosci.,* 2009, vol. 29, pp. 14394–14407.
20. Fico, A., Fiorenzano, A., Pascale, E., et al., Long noncoding RNA in stem cell pluripotency and lineage commitement: functions and evolutionary conservation, *Cell. Mol. Life Sci.,* 2019, vol. 76, pp. 1459–1471.
21. Gerdes, P., Richardson, S.R., Mager, D.L., and Faulkner, G.J., Transposable elements in the mammalian embryo: pioneers surviving through stealth and service, *Genome Biol.,* 2016, vol. 17, pp. 100–116.
22. Grammatikakis, I., Panda, A.C., Abdelmohsen, K., and Gorospe, M., Long noncoding RNAs (lncRNAs) and the molecular hallmarks of aging, *Aging* (Albany, NY), 2014, vol. 6, pp. 992–1009.
23. Guzman, H., Sanders, K., Idica, A., et al., miR-128 inhibits telomerase activity by targeting TERT mRNA, *Oncotarget,* 2018, vol. 9, pp. 13244–13253.
24. Hadjiargyrou, M. and Delihas, N., The intertwining of transposable elements and non-coding RNAs, *Int. J. Mol. Sci.,* 2013, vol. 14, no. 7, pp. 13307–13328.
25. Honson, D.D. and Macfarlan, T.S., A lncRNA-like role for LINE1s in development, *Dev. Cell*, 2018, vol. 46, pp. 132–134.
26. Ingolia, N.T., Lareau, L.F., and Weissman, J.S., Ribosome profiling of mouse embryonic stem cells reveals the complexity and dynamics of mammalian proteomes, *Cell,* 2011, vol. 147, pp. 789–802.
27. Johnson, R. and Guigo, R., The RIDL hypothesis: transposable elements as functional domains of long noncoding RNAs, *RNA,* 2014, vol. 20, pp. 959–976.
28. Kapusta, A., Kronenberg, Z., Lynch, V.J., et al., Transposable elements are major contributors to the origin, diversification, and regulation of vertebrate long noncoding RNAs, *PLoS Genet.,* 2013, vol. 9, p. e1003470.

29. Kelley, D. and Rinn, J., Transposable elements reveal a stem cell-specific class of long noncoding RNAs, *Genome Biol.,* 2012, vol. 13, no. 11, p. R107.

30. Kondo, T., Plaza, S., Zanet, J., et al., Small peptides switch the transcriptional activity of Shavenbaby during *Drosophila* embryogenesis, *Science,* 2010, vol. 329, pp. 336–339.

31. Kordyukova, M., Olovnikov, I., and Kalmykova, A., Transposon control mechanisms in telomere biology, *Curr. Opin. Genet. Dev.,* 2018, vol. 49, pp. 56–62.

32. Kour, S. and Rath, P.C., Age-dependent differential expression profile of a novel intergenic long noncoding RNA in rat brain, *Int. J. Dev. Neurosci.,* 2015, vol. 47, pp. 286–297.

33. Kour, S. and Rath, P.C., Long noncoding RNAs in aging and age-related diseases, *Ageing Res. Rev.*, 2016, vol. 26, pp. 1–21.

34. Ladoukakis, E., Pereira, V., Magny, E.G., et al., Hundreds of putatively functional small open reading frames in *Drosophila, Genome Biol.,* 2011, vol. 12, p. 118.

35. Lambowitz, A.M. and Belfort, M., Mobile bacterial group II introns at the crux of eukaryotic evolution, *Microbiol. Spectr.*, 2015, vol. 3, MDNA3-0050-2014.

36. Lauressergues, D., Couzigou, J.M., Clemente, H.S., et al., Primary transcripts of microRNAs encode regulatory peptides, *Nature,* 2015, vol. 520, no. 7545, pp. 90–93.

37. Lee, H.E., Huh, J.W., and Kim, H.S., Bioinformatics analysis of evolution and human disease related transposable element-derived microRNAs, *Life* (Basel), 2020, vol. 10, p. 95.

38. Li, L.J., Leng, R.X., and Fan, Y.G., Translation of noncoding RNAs: focus on lncRNAs, pri-miRNAs, and circRNAs, *Exp. Cell Res.,* 2017, vol. 361, pp. 1–8.

39. Li, X., Zhang, J., Yang, Y., et al., MicroRNA-340-5p increases telomere length by targeting telomere protein POT1 to improve Alzheimer's disease in mice, *Cell Biol. Int.,* 2021, vol. 45, no. 6, pp. 1306–1315. https://doi.org/10.1002/cbin.11576

40. Lou, Z., Zhu, J., Li, X., et al., LncRNA Sirt1-AS upregulates Sirt1 to attenuate aging related deep venous thrombosis, *Aging* (Albany, NY), 2021, vol. 13, pp. 6918–6935.

41. Lu, X., Sachs, F., Ramsay, L., et al., The retrovirus HERVH is a long noncoding RNA required for human embryonic stem cell identity, *Nat. Struct. Mol. Biol.,* 2014, vol. 21, pp. 423–425.

42. Lu, S., Zhang, J., Lian, X., et al., A hidden human proteome encoded by 'non-coding' genes, *Nucleic Acids Res.,* 2019, vol. 47, no. 15, pp. 8111–8125. https://doi.org/10.1093/nar/gkz646

43. Ma, J.J., Ju, X., Xu, R.J., et al., Telomerase reverse transcriptase and p53 regulate mammalian peripheral nervous system and CNS axon regeneration downstream of c-Myc, *J. Neurosci.*, 2019, vol. 39, pp. 9107–9118.

44. Magny, E.G., Pueyo, J.I., Pearl, F.M., et al., Conserved regulation of cardiac calcium uptake by peptides encoded in small open reading frames, *Science,* 2013, vol. 341, pp. 1116–1120.

45. Matsumoto, A., Pasut, A., Matsumoto, M., et al., mTORC1 and muscle regeneration are regulated by the LINC00961-encoded SPAR polypeptide, *Nature,* 2017, vol. 541, pp. 228–232.

46. Maxwell, P.H., What might retrotransposons teach us about aging, *Curr. Genet.,* 2016, vol. 62, pp. 277–282.

47. Mercer, T.R., Dinger, M.E., Sunkin, S.M., et al., Specific expression of long noncoding RNAs in the mouse brain, *Proc. Natl. Acad. Sci. U.S.A.,* 2008, vol. 105, pp. 716–721.

48. Mercer, T.R. and Mattick, J.S., Structure and function of long noncoding RNAs in epigenetic regulation, *Nat. Struct. Mol. Biol.,* 2013, vol. 20, pp. 300–307.

49. Mueller, C., Aschacher, T., Wolf, B., and Bergmann, M., A role of LINE-1 in telomere regulation, *Front. Biosci.,* 2018, vol. 23, pp. 1310–1319.

50. Mus, E., Hof, P.R., and Tiedge, H., Dendritic BC200 RNA in aging and in Alzheimer's disease, *Proc. Natl. Acad. Sci. U.S.A.,* 2007, vol. 104, no. 25, pp. 10679–10684.

51. Nelson, B.R., Makarewich, C.A., Anderson, D.M., et al., A peptide encoded by a transcript annotated as long noncoding RNA enhances SERCA activity in muscle, *Science,* 2016, vol. 351, pp. 271–275.

52. Nichuguti, N. and Fujiwara, H., Essential factors involved in the precise targeting and insertion of telomere-specific non-LTR retrotransposon, SART1Bm, *Sci. Rep.,* 2020, vol. 10, p. 8963.

53. Ng, S.Y., Bogu, G.K., Soh, B.S., and Stanton, L.W., The long noncoding RNA *RMST* interacts with SOX2 to regulate neurogenesis, *Mol. Cell,* 2013, vol. 51, pp. 349–359.

54. Park, J. and Belden, W.J., Long non-coding RNAs have age-dependent diurnal expression that coincides with age-related changes in genome-wide facultative heterochromatin, *BMC Genomics,* 2018, vol. 19, p. 777.

55. Pavlicev, M., Hiratsuka, K., Swaggart, K., et al., Detecting endogenous retrovirus-driven tissue-specific gene transcription, *Genome Biol. Evol.,* 2015, vol. 7, pp. 1082–1097.

56. Pereira Fernandes, D.P., Bitar, M., Jacobs, F.M., and Barry, G., Long non-coding RNAs in neuronal aging, *Noncoding RNA,* 2018, vol. 4, p. E12.

57. Popa, A., Labrigand, P., Barbry, R., and Waldmann, R., Pateamine A-sensitive ribosome profiling reveals the scope of translation in mouse embryonic stem cells, *BMC Genomics,* 2016, vol. 17, p. 52.

58. Qian, W., Cai, X., and Qian, Q., Sirt1 antisense long non-coding RNA attenuates pulmonary fibrosis through sirt1-mediated epithelial-mesenchymal transition, *Aging* (Albany, NY), 2020, vol. 12, pp. 4322–4336.

59. Rodriguez-Martin, B., Alvarez, E.G., Baez-Ortega, A., et al., Pan-cancer analysis of whole genomes identifies driver rearrangements promoted by LINE-1 retrotransposition, *Nat. Genet.,* 2020, vol. 52, pp. 306–319.

60. Ruiz-Orera, J., Messeguer, X., Subirana, J.A., and Alba, M.M., Long non-coding RNAs as a source of new peptide, *eLife,* 2014, vol. 3, p. e03523.

61. Schratz, K.E., Extrahematopoietic manifestations of the short telomere syndromes, *Hematol. Am. Soc. Educ. Progr.,* 2020, vol. 2020, pp. 115–122.

62. Scheidler, C.M., Kick, L.M., and Schneider, S., Ribosomal peptides and small proteins on the rise, *ChemBioChem*, 2019, vol. 20, pp. 1479–1486.

63. Schroeder, E.A., Raimundo, N., and Shadel, G.S., Epigenetic silencing mediates mitochondria stress-induced longevity, *Cell Metab.,* 2013, vol. 17, pp. 954–964.

64. Tiwari, B., Jones, A.E., Caillet, C.J., et al., P53 directly repress human LINE1 transposons, *Genes. Dev.,* 2020, vol. 34, pp. 1439–1451.

65. Trapathi, V., Shen, Z., Chakraborty, A., et al., Long noncoding RNA MALAT1 controls cell cycle progression by regulating the expression of oncogenic transcription factor B-MYB, *PLoS Genet.,* 2013, vol. 9, p. e1003368.

66. Trembinski, D.J., Bink, D.I., Theodorou, K., et al., Aging-regulated anti-apoptotic long non-coding RNA Sarrah augments recovery from acute myocardial infarction, *Nat. Commun.,* 2020, vol. 11, p. 2039.

67. Trizzino, M., Kapusta, A., and Brown, C.D., Transposable elements generate regulatory novelty in a tissue-specific fashion, *BMC Genomics,* 2018, vol. 19, p. 468.

68. Wang, H., Iacoangeli, A., Popps, S., et al., Dendritic BC1 RNA: functional role in regulation of translation initiation, *J. Neurosci.,* 2002, vol. 22, no. 23, pp. 10232–10241.

69. Wang, T., Zeng, J., Lowe, C.B., et al., Species-specific endogenous retroviruses shape the transcriptional network of the human tumor suppressor protein p53, *Proc. Natl. Acad. Sci. U.S.A.,* 2007, vol. 104, pp. 18613–18618.

70. Zhang, J., Mujahid, H., Hou, Y., et al., Plant long ncRNAs: a new frontier for gene regulatory control, *Am. J. Plant Sci.,* 2013, vol. 4, no. 5, art. ID 32139.

71. Zhao, Y., Yuan, J., and Chen, R., NONCODEv4: Annotation of noncoding RNAs with emphasis on long noncoding RNAs, in *Long Non-Coding RNAs: Methods and Protocols*, Methods Mol. Biol. Ser., vol. 1402, New York: Springer-Verlag, 2016, pp. 243–254.

Translated by A. Barkhash