Received: 21 May 2018 | Revised: 28 June 2018 | Accepted: 3 July 2018

DOI: 10.1002/agm2.12030

REVIEW ARTICLE

WILEY Aging Medicine Open Access

Role of lncRNAs in aging and age-related diseases

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Funding information
Natural Science Foundation of Hunan Province, China, Grant/Award Number: 2018JJ3759, 2018JJ3716

Abstract

Aging is progressive physiological degeneration and consequently declined function, which is linked to senescence on both cellular and organ levels. Accumulating studies indicate that long noncoding RNAs (lncRNAs) play important roles in cellular senescence at all levels—transcriptional, post-transcriptional, translational, and post-translational. Understanding the molecular mechanism of lncRNAs underlying senescence could facilitate interpretation and intervention of aging and age-related diseases. In this review, we describe categories of known and novel lncRNAs that have been involved in the progression of senescence. We also identify the lncRNAs implicated in diseases arising from age-driven degeneration or dysfunction in some representative organs and systems (brains, liver, muscle, cardiovascular system, bone pancreatic islets, and immune system). Improved comprehension of lncRNAs in the aging process on all levels, from cell to organismal, may provide new insights into the amelioration of age-related pathologies and prolonged healthspan.

KEYWORDS
age-related diseases, long noncoding RNAs, senescence

1 | INTRODUCTION

Aging is progressive physiological degeneration and consequently declined function, which is characterized by several tentative hallmarks at molecular and cellular levels.[1] Apart from genomic instability and telomere attrition, advances in aging research exhibit a lot more determinants of aging, rendering this physiological process complex and complicated. Senescence on both cellular and organ levels gradually causes age-related diseases, such as cardiovascular diseases, Alzheimer's disease (AD), cancer, and sarcopenia, most in forms of comorbidities. Meanwhile, consequent fragility and frailty result in high mortality. As world population above 60 is expected to double and reach 22% by 2050, the increases in morbidity and mortality are noted in elderly populations.[2,3] Therefore, the boosting aging global population becomes a critical healthcare issue, which demands further exploration through explicit mechanisms underlying the aging process.[4-6]

Age-related changes in the cellular proteome and transcriptome levels are indispensable in physiological alterations in cells, tissues, and organ systems during aging. Recent advancement in microarrays and sequencing techniques has lead to a better understanding of various important mammalian genomes (eg, human, rat, and mouse) and their respective cellular, tissue, and organ-specific transcriptomes. Series of multitude projects, including Functional Annotation of the Mammalian Genome and Encyclopedia of DNA elements, have revealed that only about 2% of transcripts are protein-coding RNAs, and the reminders are pervasively transcribed into myriad multifunctional forms of RNA molecules known as noncoding RNAs (ncRNAs).[7,8] Based on the transcript length, these ncRNAs are divided into small (20-30 nt) ncRNAs and long (>200 nt) ncRNAs (lncRNAs).[8] lncRNAs are poorly conserved but abundant heterogeneous regulatory ncRNAs. Based on their genomic location, orientation, and mode of transcription, they are further classified into sense, antisense, bidirectional, promoter-associated, enhancer-associated, pseudogene-associated,

telomere-associated, and circular lncRNAs in a broad but mutually nonexclusive manner.[9,10] They act as regulatory players with versatile roles in different modes. lncRNAs regulate gene expression virtually at all levels—transcriptional, RNA processing, translational, and post-translational—by interacting with DNA, RNA, or proteins[11] (Figure 1). The subcellular localization of lncRNAs may also bring additional complexity to their function.[12]

lncRNAs are increasingly recognized as essential in various cellular processes such as proliferation, apoptosis, differentiation, and senescence for the impact on gene expression.[13-18] lncRNAs also underly important pathologic processes in age-mediated function, including metabolic imbalances, neurodegeneration, and cancer.[19,20]

In this review, the emphasis is given to the association of lncRNAs with the aging process in cellular and organic levels with the forms of age-related frequently occurring diseases.

2 | lncRNAs IN CELLULAR AGING

Senescence is characterized as a stable form of growth arrest in untransformed cells, triggered by telomere attrition, chromosome destabilization, DNA damage, mitochondrial dysfunction, oncogene activation, and other cellular stress linked to cell cycle.[21] Senescent cells are featured in morphological, secretory, and molecular aspects.

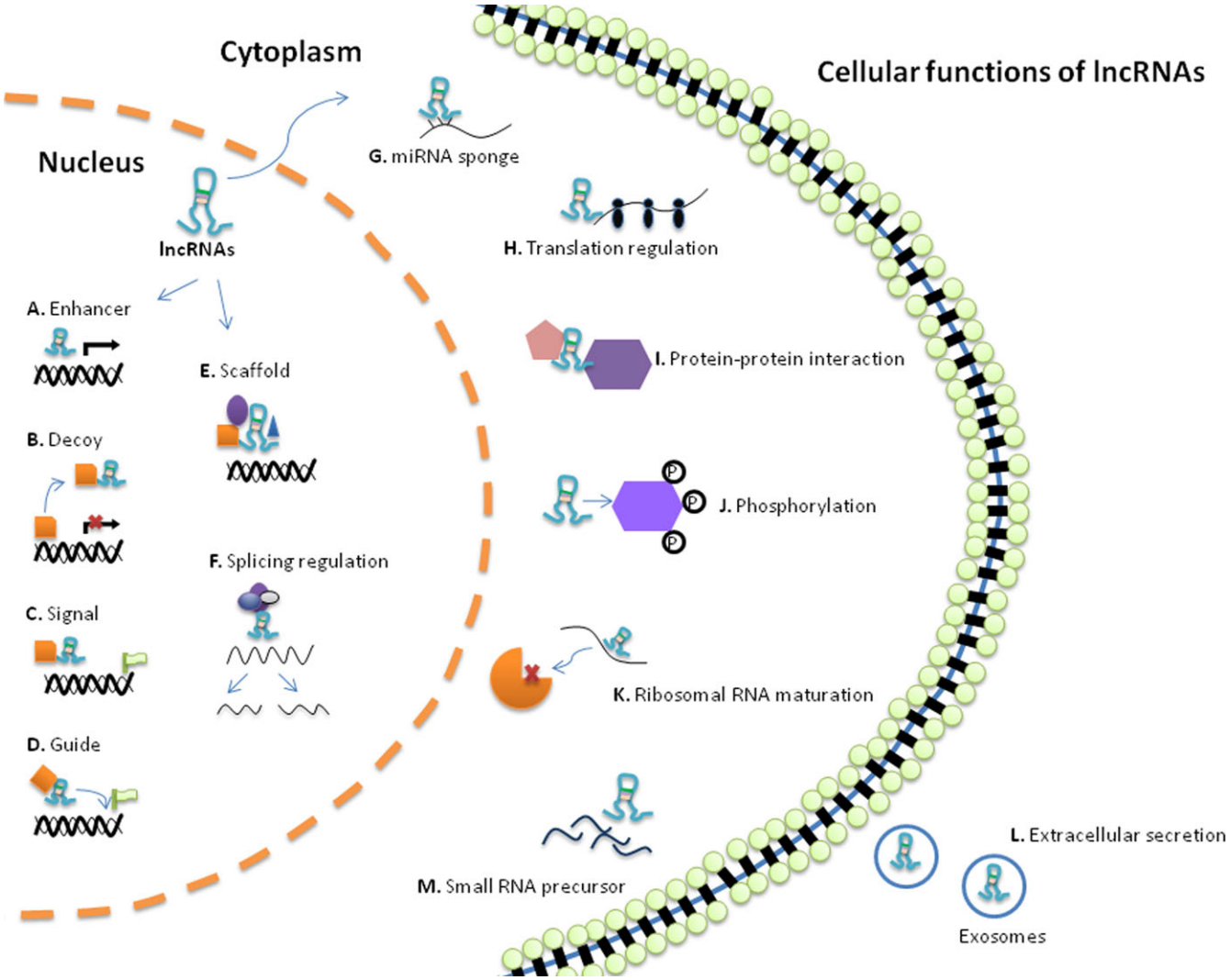

FIGURE 1 Cellular functions of long noncoding RNAs (lncRNAs). Genomic location relative to regulatory mechanisms of lncRNAs in the nucleus, cytoplasm, and extracellular compartments. Nuclear-localized lncRNAs can act as (A) enhancers to induce transcription in *cis* or in *trans*; or (B) decoy to induce transcription factors and chromatin modifiers, blocking their binding to DNA; or (C) molecular signals to activate or silence gene expression through signaling to regulatory pathways; or (D) guide to instruct transcriptional elements (eg, chromatin modifiers) to specific target sites; or (E) scaffolds, binding proteins complexes to affect gene expression, and (F) then can modulate alternative splicing of pre-mRNAs. In the cytoplasm, lncRNAs can serve as (G) microRNAs (miRNAs) sponge to block their effect and then can control (H) translational events, or (I) protein-protein interaction, or (J) protein phosphorylation and activation of signaling pathways. K, They can regulate the maturation of ribosomal RNAs. Finally, some lncRNAs can be (L) released in the form of exosomes and transferred to other cells to (M) function as precursors of miRNAs and other regulatory small RNA

Distinctive features include flattened, enlarged cell size, increased SA-β-galactosidase activity, production of senescence-associated secretory phenotype (SASP), and differential expression of senescence-associated pathways (eg, upregulated *p53*, *p21*, *p27* and downregulated *Sirt1*).[22,23] Cellular senescence is implicated in normal aging. However, pathological effects of senescent cells could influence organisms wholly due to the accumulation of them during aging.[24] These influences may possibly be on account of the following aspects: (a) impaired regeneration due to exhaustion of stem cells; (b) malfunction in tissues and organs caused by SASP; and (c) disturbed energy homeostasis resulted by various stress.[12] On the contrary, cellular senescence plays a protective role against tumorigenesis, which is consistent with the counterplay of senescence pathway with tumor response pathway. Based on this counterinteraction theory, oncogene-induced senescence (OIS) model is generally utilized. Recent studies have demonstrated that numerous lncRNAs mediate cellular senescence in different stages of the cell cycle by modulating senescence-associated pathways, such as *p53*/*p21*, *pRB*/*p16*, and *p14*.[25]

2.1 | Cell cycle–associated lncRNAs

Senescence represents a permanent withdrawal from the normal cell cycle progression in response to a diverse range of cellular stress, such as DNA damage, oxidative stress, telomere attrition, and environmental stress. Characterized cell cycle inhibitors include *p16*, *p21*, and *p53*, all of which are also senescence-related tumor suppressors. lncRNAs involved in cell cycle could possibly influence senescence and organismal aging.

2.1.1 | *MALAT1*

Transcript of metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) is a cell cycle regulator localized to the nuclear speckles.[26] Abundantly expressed in several solid tumors, *MALAT1* is involved in cancer metastasis and recurrence.[27-29] Tripathi et al firstly declared the role of *MALAT1* in cell cycle progression. He found that higher level of *MALAT1* at G1/S phase and mitosis, but lower level at G1-G2 phase.[26] Several cell line studies have further confirmed that depletion of *MALAT1* triggered G1 or G1/S arrest, thus repressing cell growth and proliferation but enhancing senescence phenotype.[25,26,30,31] However, *MALAT1*-knockout mice showed no obvious phenotype of abnormalities.[32-34] The overall studies have indicated *MALAT1* is inessential for organismal development, but might be pivotal under specific pathological or environmental condition.

2.1.2 | *ANRIL*

As an antisense to *p15*/*CDKN2B*/*CDKN2A*/*ARF* gene cluster, *ANRIL* is known to suppress the expression of *CDKN2A* ($p16^{INK4A}$, $p14^{ARF}$) and *CDKN2B* ($p15^{INK4B}$) genes in *cis*.[35] This lncRNA plays an established role in cell proliferation, senescence, and aging. Depletion of *ANRIL* in WI-38 and IMR-90 cells results in upregulation of $p15^{INK4B}$ with decreased cell growth and induced senescent phenotype.[36] Recent studies have focused on its association with inflammation.[37-39] According to the hypothesis of inflammaging, the positive link with *ANRIL* to *TNF-α* and *NF-κB* suggests the role of *ANRIL* in aging and age-related diseases, such as certain cardiovascular diseases and AD.[37,38,40,41]

2.1.3 | *7SL*

7SL has been identified in various cancers.[42] As a highly conserved cytoplasmic lncRNA with six signal recognition proteins, *7SL* forms a partial hybrid with the 3′-untranslated region of *p53* mRNA and competes with HuR protein for binding to *p53* mRNA.[43,44] *7SL* silencing studies in HeLa and HCT116 cells displayed cell cycle arrest and senescence by increasing *p53* translation through enhanced interaction between HuR and *p53* mRNA.[45]

2.1.4 | *MEG3*

Maternally expressed gene 3 (*MEG3*) is a maternally expressed and imprinted noncoding transcript.[46] This lncRNA participates in biological processes including central nervous system development, angiogenesis, and liver metabolism.[47-49] *MEG3* is highly expressed in certain normal tissues but repressed in many tumors.[48,50-52] *MEG3* affects the activities of multiple key cell cycle regulators, such as *p53*, *MDM2*, *GDF15*, and *RB1*.[53,54] Restoring the expression of *MEG3* in HeLa, C-33A, MCF-7, and H4 cell lines rightly suppressed tumor cell growth via inducting G2/M cell cycle arrest and apoptosis, while downregulating level of MEG3 enhanced autophagy, cell proliferation, and inhibited cell death.[55-57] As a tumor repressor, *MEG3* could be a potential target for cancer diagnosis and prognosis and treatment.[53] Decreased levels of *MEG3* have also been observed in some age-related neurodegenerative disorders including Huntington's disease (HD), whose mechanisms of epigenetic gene regulation in neurons may seem to contradict with those in cancer cells.[58] Detailed mechanisms on its regulation of senescence and apoptosis need further elucidation to understand the role in brain aging.

2.1.5 | *H19*

H19 is a highly conserved and maternally expressed lncRNA, whose location is near the paternally expressed insulin-like growth factor 2 (*IGF2*) genes.[59] As an epigenetic regulatory RNA, *H19* positively affects cell growth and proliferation and delays senescence, thus promoting tumorigenesis.[60-62] Due to the adjacent localization of *H19* and *IGF2* (*H19-IGF2*) genes, expressions of both genes are always balanced, which is necessary in cell growth, proliferation, senescence, and apoptosis.[63,64] Loss of imprinting at *H19-IGF2* locus has been involved in the onset of cellular senescence. Interestingly, erasure (hypomethylation) of imprinting at this locus observed in aging is accompanied by enhanced expression of *H19* but by

reduced expression of *IGF2*, which indicates longevity and low incidence of tumor growth. Contrarily, imprinting loss (hypermethylation) in aging leads to overexpression of both genes, which may correspond to a higher incidence of cancer in advanced age.[64,65] Additionally, *H19* is also associated with the development of other age-related diseases, such as fat deposition and skeletal muscle regeneration.[66,67]

2.1.6 | *UCA1*

Firstly identified in bladder transitional cell carcinoma, urothelial cancer-associated 1 (*UCA1*) has been demonstrated to promote cell proliferation and attenuate apoptosis as precursors to multiple miRNAs in malignant tumors.[68,69] As cellular senescence is considered as tumor suppression, *UCA1* overexpression could induce cellular senescence.[70] Relevant mechanism studies highlight the role of *CAPERα*/*TBX3* repressor complex, which is required to prevent senescence in primary cells and mouse embryos. Certain stress induces separation of *CAPERα* and *TBX3*, thus activating production of *UCA1* RNA, and causes senescence. Furthermore, *CAPERα*/*TBX3* is known to regulate chromatin structure and to repress transcription of $p16^{INK4A}$ and the *RB* pathway. In proliferating cells, *hsRNPA1* binds and destabilizes $p16^{INK4A}$ mRNA, whereas during senescence, *UCA1* stabilizes $p16^{INK4A}$ mRNA by sequestering *hsRNPA1* from the binding with $p16^{INK4A}$.[70,71]

2.1.7 | *FAL1*

Focally amplified lncRNA on chromosome 1 (*FAL1*) was firstly identified among somatic copy number alterations of lncRNAs in 2394 tumor specimens from 12 cancer types through a genomewide survey. *FAL1* displays striking oncogenic activity partly by suppressing *p21* through association with BM1. On the contrary, *FAL1* silencing or downregulation leads to G0/G1 arrest and cellular senescence.[72,73]

2.1.8 | *Gadd7*

Gadd7 was isolated from Chinese hamster ovary cells, whose levels were detected in response to DNA damage.[74] Overexpression of *gadd7* results in G1 arrest and promotes apoptosis by directly binding to TAR DNA-binding protein (TDP-43) and interfering with its interaction with *Cdk6* mRNA.[75] As consequent *Cdk6* degradation induces cell cycle arrest and senescent phenotype, the possible impact of *gadd7* on aging is expecting.[76]

2.1.9 | *MR31HG*

MR31HG (MIR31 host gene/*LOC554202*) is located 400 kb upstream of the $p16^{INK4A}$ locus in humans. *MR31HG* harbors miR-31, which is upregulated in senescent human umbilical vein endothelial cells (ECs) but downregulated in various cancers.[77,78] Previous studies have shown that *MR31HG* could modulate cell growth and suppress tumorigenesis via miR-31.[79-82] Interestingly but intriguingly, a recent study reported that *MR31HG* was upregulated in OIS, whereas silencing of this lncRNA promoted $p16^{INK4A}$-dependent senescence phenotype.[83] *MR31HG* is present in both nucleus and cytoplasm in presenescent cells, but then located mainly in the cytoplasm after BRAF activation. *MR31HG* binds to both $p16^{INK4A}$ and *MR31HG* genomic regions with polycomb group (PcG) proteins. During OIS, PcG proteins and enhanced *MR31HG* are required for PcG-mediated repression of $p16^{INK4A}$ locus.[83]

2.1.10 | *PANDA*

p21-associated ncRNA DNA damage activated (*PANDA*), a bidirectional transcript from the *p21* promoter induced upon DNA damage via *p53*, modulates cell proliferation, apoptosis, and senescence in human fetal lung fibroblasts and neonatal foreskin, as a decoy for pro-proliferative transcriptional factor, NF-YA.[84-86] Additionally, *PANDA* induced by *p53* results in G1 cell cycle arrest in lymphoma through inactivation of MAPK/ERK pathway.[87] Surprisingly, it has been demonstrated to determine entry and exit from senescence via dual regulation. *PANDA* at low level inhibits expressions of multiple prosenescence genes through the formation of *PANDA-SAFA-PRC-BMI* complex in proliferative cells, whereas increased *PANDA* dissociated from this complex in senescent cells induces senescence arrest by repressing proliferation-promoting genes and enforcing prosenescence genes.[88] Consistently, depletion of *PANDA* by siRNA results in exit from senescence in senescent fibroblasts.[88] The flexibility in switching between proliferation and senescence enables PANDA as a potential target for senescence and age-related intervention.

2.1.11 | *lincRNA-p21*

P53-mediated *lincRNA-p21* is firstly identified as a regulator of *p21* by recruiting hnRNP-K to the promoter region of *p21*, thus diminishing cell proliferation in mouse embryonic fibroblasts.[89,90] Meanwhile, *lincRNA-p21* is proved to provide positive feedback to *p53* transcription via interacting with multiple factors, including MDM2 and Rck.[89,91] *HuR/Ago2/let-7* complex destabilizes *lincRNA-p21* and relieves its translational inhibition on target mRNAs.[92] Further studies have found that *lincRNA-p21* impaired somatic cell reprogramming through cell senescence or apoptosis epigenetically.[89,93] This lncRNA participates in various cancers and age-related coronary artery diseases, such as atherosclerosis and myocardial infarction.[91,94-96]

2.1.12 | *PINT*

p53-induced noncoding transcript (*PINT*) is also controlled by *p53* and in turn affects *p53*, MAPK, and TGF-β signaling by PRC2-mediated modulation on relevant gene promoter regions.[97] *PINT* negatively associates with senescence and age-related diseases.[97]

2.1.13 | *TUG1*

Taurine upregulated gene 1 (*TUG1*) is primarily known as a growth regulator induced by *p53* upon DNA damage.[98,99] Apart from *p53*-mediated growth arrest and apoptosis, *TUG1* disrupts the expressions of HOX genes family (eg, *HOXB7*), which results in aging.[99] Moreover, *TUG1* controls glycolysis in proliferation and metastasis of tumor cells through regulation of hexokinase 2 via miR-455-3p/AMPKβ2.[100] As *TUG1* is highly expressed in the human subependymal zone, it has been involved in age-related neurodegenerative diseases, such as ischemic stroke and HD.[101-103] *TUG1* also has an impact on other tissue-specific aging, such as intervertebral disk and age-related cataract, through Wnt/β-catenin or caspase pathways.[104,105] *TUG1* is upregulated in the murine retina,[106] but its influence in retinal degenerative diseases is not clear.

HEIH and *HULC* are both highly expressed in hepatitis B virus-related hepatocellular carcinoma.[107-109] They are involved in tumorigenesis by promoting hepatoma cell growth and proliferation. Suppression targets for HEIH are *p15*, *p16*, *p21*, and *p57*, while the target for HULC is *p18*.[108,109] BRAF-activated noncoding RNA exerts oncogenic function in cancers via epigenetic regulation on various genes, such as *p38 MAPK*, *MEK1/2*, *ERK1/2*, *JNK*, *NF-κB*, and *p38*.[110] Abundant studies of BRAF in last 6 years have already revealed complex signaling pathways involved in tumor cell growth, proliferation, and apoptosis, yet findings on senescent phenotypes are seldom reported. As target genes for BRAF contain those involved in regulation of cell cycle and metabolism, its role in senescence calls for future exploration.

2.2 | Telomere-associated lncRNAs

Telomeres are the protective nucleoprotein caps at the end of chromosomes, which shorten with every cell division. Preservation of the telomere lengths requires telomerase reverse transcriptase combined with telomere RNA component (*TERC*).[111] Telomere attrition is characterized as a key hallmark in cellular senescence and organismal aging.[1,22] lncRNAs play roles in the organization of telomere dynamics, indicating a possible correlation with telomere-associated diseases.

2.2.1 | *TERC*

TERC functions as a template for telomeric DNA synthesis by telomerase. Its involvement in senescence and aging is probably due to gradual loss of telomerase activity. *TERC*-deficient mice displayed pulmonary premature aging and osteoporosis.[112,113] The pulmonary senescence-associated inflammatory phenotype could partly be explained by telomerase-mediated *NF-κB* transcription.[114] Introduction of *TERC* in telomerase-deficient mice was confirmed to rescue premature aging phenotypes by restoring functional telomerase.[115] Apart from that, *TERC* could affect angiogenesis and metastasis-related genes' expression without affecting telomere length.[116]

2.2.2 | *TERRA*

Since the identification of telomeric repeat-containing RNA (*TERRA*) in yeast, roles of this lncRNA have been highlighted in telomere functions throughout senescence and aging process.[117-119] *TERRA* is transcribed by RNA polymerase II in a conserved manner.[120] Altered expression of *TERRA* affects the formation of telomeric heterochromatin and the regulation of telomerase activity.[121] However, the association between telomere length and *TERRA* expression is heterogeneous according to types of cells or species observed and methods or protocols applied.[122] Therefore, conflicting results have been published on *TERRA* expression in cancers. *TERRA* levels were elevated in various cancers but decreased in advanced stages of them.[118,123,124] Again, conflicting results have been uncovered on the relationship between *TERRA* and cellular senescence. Some studies revealed that overexpression of *TERRA* triggered premature senescence by the accumulation of itself and defective telomeric recombination.[111,119,125] On the other hand, increased *TERRA* expression in telomerase-negative cells was reported to delay the onset of senescence.[126,127] Another study even found no difference in *TERRA* expression between early and late passage human primary fibroblast, even in the state of repressed telomeric maintenance during senescence.[128] The mystery of *TERRA* in senescence is expecting to be unveiled.

2.3 | Chromatin-modulating lncRNAs

Chromatin remodeling occurs within senescence and aging process. Alterations in chromatin features include epigenetic changes, heterochromatinization, histone modification, and DNA methylation. lncRNAs usually serve as modifiers, decoys, or guides, by recruiting various histone and DNA methyltransferase to the site of chromosome inactivation (eg, *Xist*, *HOTAIR*, and *lncRNA-p21*) or by directing transcriptional factors to bind with regulatory DNA elements (eg, *AIR*). Several representative lncRNAs are mentioned in the previous parts, such as *H19*, *ANRIL*, and *TERRA*. In this part, we will focus on those unmentioned related lncRNAs.

2.3.1 | *Xist*

Transcribed from the inactive X chromosome, *Xist* is responsible for gene imprinting and X chromosome inactivation in females by blocking the access of RNA polymerase II.[129,130] Level of *Xist* declines in senescent cells,[131] yet its function in senescence is unclear.

2.3.2 | *Kcnq1ot1*

KCNQ1-overlapping transcript 1 (*Kcnq1ot1*) is a paternally expressed antisense lncRNA to *Kcnq1ot1* gene.[132] It exerts an impact on nearby imprinted genes, including *CDKN1C* and *KCNQ1*, by recruiting chromatin remodeling complexes to the paternal *DMR-LIT1* locus.[133,134] As the role of *CDKN1C* in cell cycle progression, *Kcnq1ot1* affects cellular senescence and aging process. Moreover, the suppressed level of *Kcnq1ot1* is relevant to age-related diseases,

such as type 2 diabetes, atherosclerosis, myocardial infarction, and various cancers.[135-138]

2.3.3 | *ANRASSF1*

As a member of poorly characterized RNAs, *ANRASSF1* is an unspliced, nuclear-localized, intronic antisense lncRNA targeting to the tumor suppressor gene, Ras-associated domain-containing protein 1A (*RASSF1A*), which is involved in G1/S cell cycle arrest and apoptosis upon DNA damage.[139] Increasing DNA methylation of *RASSF1A* is observed in tumors, aging noncancerous liver, and chronic gastritis relevant to age.[140-142] *ANRASSF1* could reduce the transcription of *RASSF1A* by forming a DNA-RNA hybrid and recruiting PRC2 to *RASSF1A* promoter region,[139] indicating the role of *ANRASSF1* in senescence and aging.

There are another couple of lncRNAs whose target genes have unambiguous roles in senescence and age-related processes, yet the indirect involvement of these lncRNAs in the same field is not clear. Like *Air*, or antisense Igf2 receptor (Igf2r) RNA, is a paternally expressed and imprinted antisense lncRNA to maternally derived *Igf2r* promoter region.[143] *Air* controls transcription of *Igf2r* in *cis* via allele-specific methylation.[144] Igf2 is directly linked to senescence and longevity.[145,146] Another example is *ecCEBPA*, or extra coding *CEBPA*, which recruits *DNMT1* to silence *C/EBP* gene.[147] The encoded *C/EBP* family proteins could promote growth arrest by inhibiting *CDK2* and *CDK4*.[148] *C/EBP* is dramatically decreased in aged tissues and causes age-related liver injury and impaired adipogenesis and altered fat tissue function, whereas restoring aged-like isoform of *C/EBPα* favors liver proliferation.[149,150] Heterodimerization of *C/EBPβ* and *C/EBPγ* promotes cell proliferation and suppress senescence.[151] Similarly, pRNA serves to silence repeated nucleolar ribosomal RNA (rRNA) through the formation of DNA-RNA triplex and subsequent repressive DNA methylation at the rRNA promoter.[152] As levels of rRNA are tightly correlated with senescence, aging process and age-related neurodegenerative diseases (eg, AD and Werner syndrome), and symptoms (eg, depression),[153-155] the implication of pRNA in this field remains to be confirmed. *PTENpg1* negatively regulates PTEN level, the latter of which is known suppressor of senescence, aging, and tumor.

2.4 | SASP-associated lncRNAs

SASP is a critical trait of senescent cells. Also, the accumulation of senescent cells during aging provokes production of SASP factors, facilitating low-grade chronic inflammation and age-related diseases. Regulation of lncRNAs contributes to innate immune responses, such as macrophage polarization and inflammatory factor secretion.

2.4.1 | *17A*

17A controls the alternate spicing of GABA receptor and subsequent downstream signaling.[156,157] It was reported to be triggered by inflammation in AD brains, leading to increase in Aβ accumulation.[157]

2.4.2 | *FIRRE*

Functional intergenic repeating RNA element (*FIRRE*) is a newly discovered, conserved lncRNA, which has an impact on the nuclear architecture across chromosome through interacting with hnRNP-U.[158] Controlled by NF-κB signaling in macrophages, *FIRRE* positively regulates several inflammatory genes following LPS stimulation by affecting the stability of relevant mRNAs.[159]

2.4.3 | *lnc-IL7R*

lnc-IL7R is remarkably upregulated in THP-1 cells with stimulation of LPS and then, in turn, diminishes LPS-mediated proinflammatory cytokine secretion, characterized by reduced expression of E-selectin, VCAM-1, IL-6, and IL-8 through epigenetic regulation.[160] This finding indicates contribution of *lnc-IL7R* to SASP factor production.

2.4.4 | *lncRNA-LET*

lncRNA-LET (low expression in tumors) is poorly expressed in multiple tumors. Further study has shown silencing this lncRNA allows accumulation of nuclear factor 90 (NF90), the latter of which suppresses the translation of *MCP1*, *CXCL1*, and *IL-6*.[161,162] As downregulated NF90 is observed in senescent cells, *lncRNA-LET* has a positive link to low levels of SASP through actions of NF90.[162]

2.4.5 | *lincRNA-COX2*

lincRNA-COX2 is a broad-acting regulatory component of the TLR/MyD88/NF-κB pathway upon TLR activation. *lincRNA-COX2* represses transcription of a series of proinflammatory genes by interacting with *hnRNP-A/B* and *A2/B1*.[163] This lncRNA could form a complex with the switch/sucrose nonfermentable to modulate the assembly of *NF-κB* and subsequently transactivate downstream inflammatory response genes.[164] *lincRNA-COX2* enhances TLR-induced IL-6 and simultaneously suppressing chemokines CCL5, the latter of which is still controversial.[163,164]

2.4.6 | *Lethe*

The pseudogene, Lethe, is selectively induced by *TNF-α* and IL-1β upon *NF-κB* activation. On the other hand, Lethe regulates *NF-κB* pathway by interacting with the *NF-κB* subunit p65 (*RelA*) to inhibit DNA binding to downstream cytokines genes.[165] Age-related reduction in *Lethe* could be explained by increased *NF-κB* in aging tissues.[166]

2.4.7 | *NEAT1*

Localized in nucleus' interchromatin space, nuclear-enriched abundant transcript 1 (*NEAT1*) is an essential component of nuclear paraspeckles.[167] Paraspeckles can sequester many transcripts or multifunctional protein complex in the nucleus, and inhibit the

translation or biological activity of these captives. *NEAT1* serves as a novel inflammatory regulator by affecting the formation of paraspeckles.[168] *NEAT1* facilitates the expression of *IL-8* by relocating SFPQ, a repressor of IL8 transcription, to the paraspeckles.[169] *NEAT1* partly mediates LPS-induced cytokine expressions via the NF-κB pathway, as well as TLR4-activated inflammatory process via MAPK pathway.[170,171] Recent studies have revealed the involvement of *NEAT1* in osteoarthritis (OA) and formation and inflammation of foam cells,[172,173] suggesting its potential role in age-related treatment.

2.4.8 | *PACER*

p50-associated *COX-2* extragenic RNA (*PACER*) is expressed in the upstream region of *COX-2* and regulates *COX-2* expression in monocyte-derived cells upon LPS stimulation. *PACER* is modulated by CTCF/cohesion complex, which favors *PACER* transcription, and in turn, *PACER* functions to activate COX-2 expression by directly sequestering the repressive *NF-κB* p50 subunit from the *COX-2* promoter.[174] *PACER* is reported to be induced in OA chondrocytes by multiple proinflammatory cytokines, suggesting its involvement in inflammation-driven age-related diseases.[175]

2.4.9 | *THRIL*

Identified in human monocyte cell line THP1 macrophages, *TNF* and *hnRNPL*-related immunoregulatory lincRNA (*THRIL*) promotes TNF transcription by forming *THRIL-hsRNPL* complex through binding to *TNF* promoter.[176]

2.5 | Other lncRNAs in cellular aging

2.5.1 | *HOTAIR*

HOX transcript antisense RNA (*HOTAIR*) has been involved in senescence via multiple mechanisms. Transcribed from intergenic region between *HOXC11* and *HOXC12* within the homeobox (*HOXC*) gene cluster, HOTAIR regulates genes on *HOXC* foci epigenetically by acting as a scaffold and guide for various histone modification complexes.[177-179] *HOTAIR* can activate senescence through NF-κB pathway after DNA damage and even maintains the activation of this pathway in the presence of a positive feedback loop.[180] *HOTAIR* can be suppressed by *HuR* in the way similar to *lincRNA-p21*.[181] As *HOTAIR* is upregulated in senescent cells, HuR deficiency in various cells leads to dramatically increased *HOTAIR* expression, characteristic senescent phenotypes, and *HOTAIR*-mediated ubiquitination and proteolysis of ataxin-1 and snurportin-1.[181] Yet, the role of protein ubiquitination and degradation in cellular senescence is still unknown.

2.5.2 | *ASncmtRNA-2*

Mitochondria play a significant role in the onset of senescence, as accumulated mitochondrial-derived ROS induces senescence by adaptive modulation on the transcription of nuclear-encoded factors.[182] Antisense noncoding mitochondrial RNA-2 (*ASncmtRNA-2*) is exported from mitochondria to nucleus, whose flow direction is consistent with the mitochondria retrograde signaling. This lncRNA is involved in replicative senescence in ECs by maintaining the cell cycle arrest in G2/M phase through the production of *has-miR-4485* and *has-miR-1973*. Meanwhile, *p16* displayed similar *ASncmtRNA-2* pattern in the senescent cells, suggesting a possible coregulation of the two genes.[183] Expression of *ASncmtRNA-2* was preponderant in aged murine aortas,[183] indicating its impact on vascular aging.

3 | SPECIFIC EXPRESSION Of lncRNAs IN DIFFERENT TISSUES/ORGANS DURING AGING

Changes in morphology and physiology determine specific age-related diseases in different tissues and organs. We firstly summarized the various changes and characterized diseases found in the elderly. Then, we reviewed the reported specific expressed lncRNAs according to the localization or diseases (Table 1).

3.1 | Brain

Brain aging is characterized by declined cognition, reduced neurogenesis, and neurodegeneration. Neurogenesis occurs even in adult life, but generally declines throughout aging. Current studies have revealed multiple functions of lncRNAs in embryonic and adult neurogenesis from different species (eg, *MALAT1*, *TUG1*, *RMST*, *Dlx1as*, *Six3os*, *Pnky*, *TERC*, and *TERRA*). Firstly, lncRNAs influence self-renewal of neural stem cells (NSCs) and amplification of intermediated progenitors and neuroblasts. Secondly, lncRNAs determine the fate specification of NSCs, as this progenitor can generate astrocytes and oligodendrocytes, aside from neuroblasts. Lastly, lncRNAs are known key regulators of telomere dynamics in NSCs.

Impaired cognition is supposed to be a direct consequence of the alterations in synaptic connectivity.[184] lncRNAs modulate pathological protein aggregation, and the subnuclear compartment-specific lncRNAs regulate neuronal splicing, transcription, and sponging of ion channels in aging (detailed lncRNAs seen in Figure 1). Relative abundance of specific lncRNAs allows for beneficial functional processes. On the contrary, shifts in their abundance may trigger alterations in pretranscriptional and post-transcriptional regulations of neuronal genes and consequent age-related neurodegenerative diseases, including AD and Parkinson's disease (PD), which are featured by impaired cognitive and motor function. In AD, lncRNAs are known to contribute to Aβ aggregation and dysregulated synaptic plasticity. Certain differentially expressed antisense lncRNAs, including *BACE1-AS*, *SORL1-AS*, *UCHL1-AS*, and *LRP1-AS*, modulate expression or splicing of proteins involved in the generation and trafficking of Aβ.[185-188] On the other hand, *17A* is involved in Aβ accumulation through local inflammatory responses.[157] *ANRIL* regulates the expression of CDKN2B that accumulates in neurofibrillary tangles

TABLE 1 List of lncRNAs potentially implied in the aging process and age-related diseases

lncRNAs (References)	Samples studied	Processes	Effect during aging or other implications
Six3os, *Dlx1as*[258]	Adult mice brain	Neurogenesis	Upregulated in neuroblasts; downregulated in NSCs
Pnky[259]	Postnatal mice brain	Neurogenesis	Depletion of *Pnky* potentiates neuronal lineage commitment
MALAT1, *GOMAFU*, *NEAT1*, *TUG1*[101]	Human brain	Neurogenesis	Upregulated in the subependymal zone with age
RMST[260]	Human cell line	Neurogenesis	Required to promote neuronal differentiation
TERC[261]	Embryonic and postnatal mice brain	Neurogenesis	Balanced pattern with telomerase reverse transcriptase to determine NSC proliferation and survival
TERRA[123]	Postnatal mice brain	Neurogenesis	Upregulated in proliferating cerebellar neuronal progenitors
BC200[190,262–264]	Rat/human brain, cell line	Cognitive decline	Act as a scaffold to bind with translational factors to repress neuronal protein synthesis; downregulated in the aged brain; upregulated in aging brain
BC1[262–265]	Rat brain, human cell line	Cognitive decline	Act as a scaffold to bind with translational factors to repress neuronal protein synthesis; maintain neuronal excitability, mood, and exploratory behavior
BDNF-AS, *GDNF-AS*, *EPHB2-AS*[266]	Mice brain, human brain neurons	Cognitive decline	Suppress protein synthesis (BDGF, GDNF, and EPHB2) involved in neurite elaboration
GOMAFU[267]	Human brain	Cognitive decline	Instruct alternate splicing in synaptic plasticity
NEAT1[268]	Mice brain	Cognitive decline	Modulate ion channel components
BACE1-AS[186]	Human and Mice brain	Neurodegeneration	Modulate BACE1 expression and Aβ aggregation
SORL1-AS[187]	Human brain	Neurodegeneration	Direct alternate splicing of SORL1 and Aβ formation
UCHL1-AS[188,269,270]	Human brain	Neurodegeneration	Regulate UCHL1 expression, which facilitates pathogenic protein aggregation in AD and PD
LRP1-AS[185,271]	Human brain	Neurodegeneration	Regulate LRP1 expression and Aβ metabolism in AD
17A[157]	Human brain, cell line	Neurodegeneration	Induce alternate splicing of GABA protein isoform Enhance Aβ secretion in AD
ANRIL[189]	Human brain	Neurodegeneration	Regulate CDKN2B expression, which is accumulated in neurofibrillary tangles and amyloid plaques in AD
SNHG1[191]	Mice brain, human cell line	Neurodegeneration	Promote α-synuclein in PD by targeting miR-15b-5p
G069488[192]	Human cell line	Neurodegeneration	Regulate neurite regeneration and neural restoration by suppressing NEDD9 under α-synuclein accumulation in AD
RP11-142J21.2[192]	Human cell line	Neurodegeneration	Promote apoptosis by suppressing SEMA6D via MAPK under α-synuclein accumulation in AD
NEAT1, *MEG3*, *Rian*, *Mirg*[198]	Mice liver	Liver aging	Upregulated in healthy aging liver
H19[60,67]	Mice cell line	Myogenesis	Modulate myoblast differentiation and muscle regeneration
lncMD1[202,203]	Mice cell line	Myogenesis	Modulate myoblast differentiation during aging
SIRT1-AS[206]	Mice cell line	Myogenesis	Modulate myoblast differentiation
MALAT1[204,205]	Mice muscle, Mice and human cell	Myogenesis	Promote myoblast proliferation and differentiation in aging muscle
YY1[209]	Mice cell line	Myogenesis	Upregulated in myoblasts but downregulated during differentiation Regulate myogenesis at the transcriptional level
Glt2/Meg3[210]	Mice cell line	Myogenesis	Maintain muscle development
MAR1[208]	Mice cell line	Myogenesis	Attenuate muscle atrophy induced by aging
MALAT1[212-216]	Human and mice cell	Angiogenesis, v ascular remodeling	Control EC proliferation and senescence; mediate angiogenesis and vascular inflammation
MEG3[217,218]	Mice vessel, human cell	Angiogenesis	Upregulated in senescent ECs; depletion of *MEG3* promotes sprouting and EC proliferation
ANRIL[219-223]	Human artery and cell	Atherosclerosis	Distinct modulation on VSMC proliferation and plaque formation according to different splicing variants

(Continues)

TABLE 1 (Continued)

lncRNAs (References)	Samples studied	Processes	Effect during aging or other implications
H19[272–274]	Rat artery, human cell	Atherosclerosis	Modulate EC and VSMC proliferation and homeostasis
ASncmtRNA-2[183]	Mice cell	Vascular aging	Upregulated in aortas from aged mice and senescent ECs
HOTAIR[225]	Human artery, cell line	Atherosclerosis	Downregulated in ECs form atherosclerotic plaques; regulate EC proliferation and migration
MIAT[224]	Rat artery, human cell	Angiogenesis	Regulate EC function
TUG1[226,227]	Rat and mice cell	Atherosclerosis	Regulate EC apoptosis and VSMC homeostasis
linc-p21[91,95,228]	Mice cell	Atherosclerosis	Promote apoptosis and suppress proliferation in VSMCs and macrophages
Gas5[229-231]	Rat artery, human cell	Atherosclerosis, vascular remodeling	Promote VSMC proliferation and migration; guide macrophage polarization
HOXC-AS[232]	Human artery	Atherosclerosis	Downregulated in atherosclerotic plaques through inflammatory responses
linc00305[233]	Human cell	Atherosclerosis	Promote monocyte activation and vascular inflammation
lncRNA *OTTHUMT00000387022*[234]	Human plasma and cell,	Atherosclerosis	Promote inflammation in macrophages
lncRNA *RP5-833A20.1*[275]	Mice artery and cell	Atherosclerosis	Regulated cholesterol homeostasis and inflammatory responses in foam cells
H19[235]	Human cell	Osteogenesis	Promote osteoblast differentiation
MALAT1[236]	Human cell	Osteogenesis	Induce osteogenic differentiation
HOTAIR[237]	Human cell	Osteogenesis	Suppress osteogenic differentiation
DANCER[238]	Human cell	Osteogenesis	Suppress osteogenic differentiation
MEG3[239,240]	Human cell	Osteogenesis	Suppress osteogenic differentiation
MIAT[241]	Human cell	Osteogenesis	Suppress osteogenic differentiation under inflammation
MIR31HG[242]	Human cell	Osteogenesis	Rescue osteogenic differentiation inhibited by inflammation
DANCER[238,243]	Human bone and cell	Osteoporosis	Promote osteoblast differentiation; suppress osteogenic differentiation
H19[107]	Mice tissue	Lipid deposition	Imprint IGF2 and affect lipid deposition
PLUTO[251]	Human islets	T2DM	Regulate β-cell function and pancreatic formation
βlinc1[252]	Mice islets	T2DM	Associated with β-cell loss
HI-LNC901[253]	Human islets	T2DM	Correlated with insulin exocytosis
Kcnq1ot1, *HI-LNC78*, *HI-LNC80*[254]	Human islets	T2DM	Upregulated in T2DM Sense blood glucose level
HI-LNC45[254]	Human islets	T2DM	Downregulated in T2DM Sense blood glucose level

AD, Alzheimer's disease; ECs, endothelial cells; NSCs, neural stem cells; PD, Parkinson's disease; VSMCs: vascular smooth muscle cells.

and amyloid plaques in AD brain.[189] Expression of *BC200* was decreased in the normal aging brain, but elevated in AD brain.[190] The accumulated pathological protein in PD brain is α-synuclein, contained in Lewy body. The identified genes involved in PD pathology include *Parkin*, *PINK1*, *PARK-7*, and *LRRK2*. Therefore, further investigations regarding lncRNAs targeting these genes or linked to the pathogenesis of α-synuclein would be a promising strategy in PD therapy.[103,188,191,192]

3.2 | Liver

Liver blood flow is estimated to be reduced by 20%-40%, which seems to be consistent with the shrinkage of liver volume.[193,194] Accumulated lipofuscin in hepatocytes contributes to chronic oxidative stress, and vacuolation of hepatocyte nuclei is linked to diabetes and nonalcoholic fatty liver diseases (NAFLD), both of which are possible markers of hepatocyte senescence.[195,196] Age-related decline in drug metabolism and regeneration capacity, and abnormal immune responses enhance vulnerability to acute liver injury, liver fibrosis, hepatitis C, NAFLD, alcoholic liver diseases, and liver tumor. Alterations in C/EBP family and telomere reverse transcriptase by repressive chromatin remodeling are observed in aged drug-induced liver injury, resulting in impaired regenerative capacity and fibrosis.[197] A group of differentially expressed lncRNAs in mouse have been identified in the above pathophysiologies, including *NEAT1*, *MEG3*, *Rian*, and *Mirg*.[198] *Rian* and *MEG3* could regulate proliferation

by directly recruiting PRC2.[199] Mirg could predict certain cell cycle factors, such as *Myc* and *p53*.[200] Moreover, the involvement of *ANRASSF1*, *ecCEBPA*, and some other lncRNAs, whose target genes are involved in liver metabolism, cell cycle, or local inflammatory responses, remains to be elucidated.

3.3 | Muscle

Muscle mass declines progressively during aging. Sarcopenia is a common age-related skeletal muscle degeneration, characterized by reduced muscle mass and muscle fibers. The underlying mechanisms are multifaceted, including a sedentary lifestyle, reduced hormonal level, and increased inflammation, loss of proteostasis, and mitochondrial dysfunction.[201] *H19* is implicated in skeletal muscle differentiation by acting as a molecular sponge to bind the *miRlet-7*.[60] *H19* is highly expressed in skeletal muscle, as well as *H19*-encoded miRNAs, *miRlet-7*, and *miRlet-7* during muscle regeneration, all of which are regulated by SMAD1/5.[67] The muscle-specific *lncMD1* exerts as a decoy for miR-133 and miR-135, which is enhanced by *HuR*, to limit its impact on the expression of Elavl1 in muscle differentiation during muscle aging. *HuR* plays a direct role in muscle wasting and sarcopenia.[202,203] Stimulated by myostatin, *MALAT1* regulates muscle cell proliferation and differentiation, thus influencing muscle aging.[204,205] *SIRT1-AS* was recently reported to play a role in myogenesis, as its antisense target *SIRT1* could prevent senescence and aging through myogenic program.[206,207] There are other lncRNAs involved in myogenesis, such as *YY1*, *Glt2/Meg3*, and *MAR1*, whose function in muscle aging needs further exploration.[208-210]

3.4 | Cardiovascular system

Cardiovascular aging is generally accompanied by the occurrence of ischemic cardiovascular diseases (eg, hypertension, coronary artery disease [CAD], atherosclerosis, myocardial infarction, stroke).[211] An expanding number of lncRNAs have been identified in the series of pathophysiologies by regulating EC and vascular smooth muscle cell (VSMC) proliferation, angiogenesis, vascular remodeling, macrophage polarization, and cholesterol metabolism.[49] *MALAT1* is significantly important in promoting EC proliferation, vessel outgrowth, and sprouting and in protecting ECs against apoptosis induced by oxygen-glucose deprivation and ox-LDL–related inflammation via various targets (eg, miR-22-3p and encoded genes CXCR2 and Akt, miR-26a) through multiple signaling, including *p21*, *p38*, PI3K/Akt.[212-216] *MEG3* is upregulated during vascular aging. Silencing *MEG3* could prevent aging-mediated inhibition of sprouting activity and EC proliferation.[217,218] *ANRIL* is known as an independent risk factor for CAD. However, functional annotation of this lncRNA in atherosclerosis is controversial, as different splicing variants of *ANRIL* might play distinct roles.[219-223] Also, *H19*, *ASncmtRNA-2*, *HOTAIR*, *MIAT*, *TUG1*, *linc-p21*, and *Gas5* play similar roles in angiogenesis and atherosclerosis by regulating the function of ECs and VSMCs.[91,95,183,224-231] On the other hand, lncRNAs including *HOXC-AS*, *Gas5*, *linc00305*, lncRNA *OTTHUMT00000387022*, and lncRNA *RP5-833A20.1* could activate macrophages, mediate inflammatory responses, or regulate lipid metabolism, exerting impacts on atherosclerotic plaque formation.[232-234] Additionally, other lncRNAs related to macrophage activation and polarization, which are mentioned in the previous part, such as *PACER*, *THRIL*, and *lincRNA-COX2*, might be conducible to the progression of atherosclerosis.

3.5 | Bone

The process of aging breaks the balance between bone formation and resorption. The changes in bone turnover cause osteoporosis, which can also be induced by endogenous estrogen deficiency or corticosteroid treatment. Plentiful lncRNAs have already been revealed to take part in osteogenesis ossification (eg, *H19*, *MALAT1*, *HOTAIR*, *DANCR*, *MEG3*, *MIAT*, and *MIR31HG*) and osteoclast differentiation (eg, *DANCER*) via specific target mRNAs or miRNAs.[235-242] *DANCER* is involved in the pathology of osteoporosis, as it promotes inflammation-induced osteoclastogenesis and suppresses osteogenic differentiation, which implies a potential biomarker for osteoporosis.[238,243] As the half-lives of lncRNAs are less than those of mRNAs, recent strategies have applied the systematic analysis of lncRNAs-miRNAs-mRNAs regulatory network as to search for more potential biomarkers for osteoporosis.[244] Only a handful of lncRNAs have been screened out in these studies, including *LOC105376834*, *LOC101929866*, and *mmu_12821_PI428960544*, all of whose biological significances are required to be addressed in further studies.[245,246]

3.6 | Adipose tissue

Adipose tissue exerts immune and endocrine actions throughout life, besides being a major source of energy source. Compared to the subcutaneous distribution in adult years, visceral redistribution, and ectopic deposition in liver, bone marrow and muscle are adopted in the old age. lncRNAs is involved in this extensive remodeling process by controlling adipogenesis and lipid metabolism. H19 affects fat deposition and metabolism. In adult mice, low expressed IGF2 is associated with increased lipid deposition. Then during aging, the expression of *H19-IGF2* is enhanced due to loss of imprinting of this gene locus.[66] *linc-DMRT2* and *linc-TP53I13* were reported to be downregulated by lipopolysaccharide in adipose tissue of obese humans, providing clues to age-related diseases derived from interrupted homeostasis of adipose tissue.[247] Sun et al firstly identified a group of lncRNAs, termed as *lnc-RAP-n*, which are specifically regulated during adipogenesis through PPARγ and CEBPα. However, the direct impacts of individual *lnc-RAP-n* on adipose tissue aging warrant further study.[248]

3.7 | Pancreatic islets

Type 2 diabetes mellitus (T2DM) is considered as an age-related disease, as it is well documented that aging is associated with declined insulin action and β-cell secretory activity.[249] Moreover, pancreatic islet cell senescence partly contributes to the rise of T2DM in the elderly.[250] Growing evidence implicates lncRNAs in the etiology of

T2DM. *PLUTO* is involved in pancreas development and β-cell function, as it regulates PDX1 transcriptional activity.[251] *βlinc1*, a β-cell long intergenic noncoding RNA, could modulate β-cell formation and function.[252] *HI-LNC901* was reported to be directly correlated with insulin exocytosis.[253] In addition, high levels of *Kcnq1ot1*, *HI-LNC78*, and *HI-LNC80* and low level of *HI-LNC45* were observed in pancreatic islets from diabetic individuals or in the presence of high glucose, indicating the function of sensing blood glucose levels.[254]

3.8 | Immune system

Immunosenescence refers to the acquisition of senescent features in the immune system, which result in increased susceptibility to infection and a higher incidence of age-related diseases. Moreover, aging is considered as a low-grade chronic inflammation state, termed inflammaging, where SASP plays an important role.[255] SASP-associated lncRNAs have been stated above in Section 2.4. Apart from that, loss of $CD4^+$T cells partly leads to dysfunction of innate immunity. Only limited lncRNAs, such as linc-MAF-4 and rmrp, post-transcriptionally regulated $CD4^+$T-cell subsets, but no direct or indirect evidences point to their involvement in aging.[256,257]

4 | CONCLUSION AND PERSPECTIVES

As concluding remarks, the emerging role of lncRNAs as regulators of cellular senescence and age-related diseases is still in its infancy. Numerous diseases arise with advancing age, yet we just pick a couple of them to discuss in our review. Cancer is another kind of age-related disease, in which the function of lncRNAs has been deeply investigated; thus, it is difficult for us to list all of them in limited words. At present, aging and age-related diseases have become a heavy burden in society. Illustrating lncRNAs function in aging physiology and pathology is of great significance under this context. Samples from elderly populations and a few animal models are adopted to obtain the comprehensive spectrum of lncRNAs implicated in age-associated diseases. On the other hand, applications of recent advanced technologies facilitate detailed elucidation of mechanisms on the regulation and function of lncRNAs systematically. Although the potential usefulness of lncRNAs in aging and age-related diseases cannot be fully realized at present, we can expect fast progress in technologies will enable us to make good use of lncRNAs in aging.

ACKNOWLEDGMENTS

This work was financially supported by the Natural Science Foundation of Hunan Province, China (2018JJ3759 and 2018JJ3716).

CONFLICT OF INTEREST

The authors declared no conflict of interests regarding this manuscript.

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How to cite this article: He J, Tu C, Liu Y. Role of lncRNAs in aging and age-related diseases. *Aging Med*. 2018;1:158–175. https://doi.org/10.1002/agm2.12030