ROLE OF INCRNAs IN AGING AND AGE-RELATED DISEASES

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INTRODUCTION

Aging is progressive physiological degerenation and consequently declined function, which is characterized by several tentative hallmarks at molecular and cellular levels. 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. Therefore, the boosting aging global population becomes a critical healthcare issue, which demands further exploration through explicit mechanisms underlying the aging process.

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). Based on the transcript length, these ncRNAs are divided into small (20-30 nt) ncRNAs and long (>200 nt) ncRNAs (lncRNAs). 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. 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 (Figure 1). The subcellular localization of lncRNAs may also bring additional complexity to their function.

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

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. 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 (J) protein-protein interaction, or (K) 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 RNAs.
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). 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. 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.

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. Abundantly expressed in several solid tumors, MALAT1 is involved in cancer metastasis and recurrence. 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. 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. However, MALAT1-knockout mice showed no obvious phenotype of abnormalities. 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

Suppression of ANRIL in WI-38 and IMR-90 cells results in upregulation of p15

with decreased cell growth and induced senescent phenotype. Recent studies have focused on its association with inflammation. According to the hypothesis of inflammaging, the positive link with ANRIL to TNF-α and NF-xB suggests the role of ANRIL in aging and age-related diseases, such as certain cardiovascular diseases and AD.

2.1.3 7SL

7SL has been identified in various cancers. 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. 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.

2.1.4 MEG3

Maternally expressed gene 3 (MEG3) is a maternally expressed and imprinted noncoding transcript. This IncRNA participates in biological processes including central nervous system development, angiogenesis, and liver metabolism. MEG3 is highly expressed in certain normal tissues but repressed in many tumors. MEG3 affects the activities of multiple key cell cycle regulators, such as p53, MDM2, GDF15, and RB1. 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. As a tumor suppressor, MEG3 could be a potential target for cancer diagnosis and prognosis and treatment. 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. 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. As an epigenetic regulatory RNA, H19 positively affects cell growth and proliferation and delays senescence, thus promoting tumorigenesis. 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. 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 IG2, 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. Additionally, H19 is also associated with the development of other age-related diseases, such as fat deposition and skeletal muscle regeneration.

### 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. As cellular senescence is considered as tumor suppression, UCA1 overexpression could induce cellular senescence. Relevant mechanism studies highlight the role of UCA1 RNA, and causes senescence. Furthermore, UCA1/RB3X is known to regulate chromatin structure and to repress transcription of p16INK4A and the RB pathway. In proliferating cells, hsRNPA1 binds and destabilizes p16INK4A mRNA, whereas during senescence, UCA1 stabilizes p16INK4A mRNA by sequestering hsRNPA1 from the binding with p16INK4A.

### 2.1.7 | FAL1

Focally amplified IncRNA on chromosome 1 (FAL1) was firstly identified among somatic copy number alterations of IncRNAs 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.

### 2.1.8 | Gadd7

Gadd7 was isolated from Chinese hamster ovary cells, whose levels were detected in response to DNA damage. 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. As consequent Cdk6 degradation induces cell cycle arrest and senescent phenotype, the possible impact of gadd7 on aging is expecting.

### 2.1.9 | MR31HG

MR31HG (MIR31 host gene/LOC554202) is located 400 kb upstream of the p16INK4A locus in humans. MR31HG harbors miR-31, which is upregulated in senescent human umbilical vein endothelial cells (ECs) but downregulated in various cancers. Previous studies have shown that MR31HG could modulate cell growth and suppress tumorigenesis via miR-31. Interestingly but intriguingly, a recent study reported that MR31HG was upregulated in OIS, whereas silencing of this lncRNA promoted p16INK4A, dependent senescence phenotype. 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 p16INK4A and MR31HG genomic regions with polycomb group (PcG) proteins. During OIS, PcG proteins and enhanced MR31HG are required for PcG-mediated repression of p16INK4A locus.

### 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. Additionally, PANDA induced by p53 results in G1 cell cycle arrest in lymphoma through inactivation of MAPK/ERK pathway. Surprisingly, it has been demonstrated to determine entry and exit from senescence via dual regulation. PANDA at low level inhibits expressions of multiple prosenescent genes through the formation of PANDA-SFARA-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 prosenescent genes. Consistently, depletion of PANDA by siRNA results in exit from senescence in senescent fibroblasts. 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. Meanwhile, lincRNA-p21 is proved to provide positive feedback to p53 transcription via interacting with multiple factors, including MDM2 and Rck. HuR/Ago2/let-7 complex destabilizes lincRNA-p21 and relieves its translatational inhibition on target mRNAs. Further studies have found that lincRNA-p21 impaired somatic cell reprogramming through cell senescence or apoptosis epigenetically. This IncRNA participates in various cancers and age-related coronary artery diseases, such as atherosclerosis and myocardial infarction.

### 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. PINT negatively associates with senescence and age-related diseases.
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, HOX87), 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/AMPK\(^{10}\). 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/\(\beta\)-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.\(^{106,109}\) 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-\(\kappa\)B, 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 IncRNAs

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.\(^{112-114}\) IncRNAs 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-\(\kappa\)B 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 IncRNA 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 IncRNAs

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

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

KCQ1N1-overlapping transcript 1 (Kcnq1ot1) is a paternally expressed antisense IncRNA 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 IncRNA 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 IncRNAs whose target genes have unambiguous roles in senescence and age-related processes, yet the indirect involvement of these IncRNAs in the same field is not clear. Like Air, or antisense Igf2 receptor (Igf2r) RNA, is a paternally expressed and imprinted antisense IncRNA 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 CEBP gene.147 The encoded CEBP family proteins could promote growth arrest by inhibiting CDK2 and CDK4.148 CEBP 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 CEBPα favors liver proliferation.149,150 Heterodimerization of CEBPβ and CEBPγ 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 IncRNAs

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 IncRNAs 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 Aβi accumulation.157

2.4.2 | FIRRE

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

2.4.3 | Inc-IL7R

Inc-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 Inc-IL7R to SASP factor production.

2.4.4 | IncRNA-LET

IncRNA-LET (low expression in tumors) is poorly expressed in multiple tumors. Further study has shown silencing this IncRNA 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, IncRNA-LET has a positive link to low levels of SASP through actions of NF90.162

2.4.5 | lncRNA-COX2

lncRNA-COX2 is a broad-acting regulatory component of the TLR/MyD88/NF-xB pathway upon TLR activation. lncRNA-COX2 represses transcription of a series of proinflammatory genes by interacting with hnRNPA/B and A2/B1.163 This IncRNA could form a complex with the switch/sucrose nonfermentable to modulate the assembly of NF-xB and subsequently transactivate downstream inflammatory response genes.164 lncRNA-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-xB activation. On the other hand, Lethe regulates NF-xB pathway by interacting with the NF-xB subunit p65 (RelA) to inhibit DNA binding to downstream cytokines genes.165 Age-related reduction in Lethe could be explained by increased NF-xB 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.\textsuperscript{168} NEAT1 facilitates the expression of IL-8 by relocating SFPQ, a repressor of IL8 transcription, to the paraspeckles.\textsuperscript{169} NEAT1 partly mediates LPS-induced cytokine expressions via the NF-κB pathway, as well as TLR4-activated inflammatory process via MAPK pathway.\textsuperscript{170,171} Recent studies have revealed the involvement of NEAT1 in osteoarthritis (OA) and formation and inflammation of foam cells,\textsuperscript{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/cohesin 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.\textsuperscript{174} PACER is reported to be induced in OA chondrocytes by multiple proinflammatory cytokines, suggesting its involvement in inflammation-driven age-related diseases.\textsuperscript{175}

2.4.9 | THRIL

Identified in human monocyte cell line THP1 macrophages, TNF and hnRNPL-related immunoregulatory lncRNA (THRIL) promotes TNF transcription by forming THRIL-hsRNPL complex through binding to TNF promoter.\textsuperscript{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 (HOX) gene cluster, HOTAIR regulates genes on HOX foci epigenetically by acting as a scaffold and guide for various histone modification complexes.\textsuperscript{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.\textsuperscript{180} HOTAIR can be suppressed by HuR in the way similar to lincRNA-p21.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{183} Expression of ASncmtRNA-2 was preponderant in aged murine aortas,\textsuperscript{184} 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, Six3as, 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.\textsuperscript{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 IncRNAs, including BACE1-AS, SORL1-AS, UCHL1-AS, and LRP1-AS, modulate expression or splicing of proteins involved in the generation and trafficking of Aβ.\textsuperscript{185-188} On the other hand, 17A is involved in Aβ accumulation through local inflammatory responses.\textsuperscript{157} ANRIL regulates the expression of CDKN2B that accumulates in neurofibrillary tangles...
| IncRNAs (References) | Samples studied | Processes | Effect during aging or other implications |
|----------------------|-----------------|----------|----------------------------------------|
| Six3os, Dlk1as258     | Adult mice brain | Neurogenesis | Upregulated in neuroblasts; downregulated in NSCs |
| Pnky259              | Postnatal mice brain | Neurogenesis | Depletion of Pnky potentiates neuronal lineage commitment |
| MALAT1, GOMAFU, NEAT1, TUG1101 | Human brain | Neurogenesis | Upregulated in the subependymal zone with age |
| RMs260               | Human cell line | Neurogenesis | Required to promote neuronal differentiation |
| TERC261              | Embryonic and postnatal mice brain | Neurogenesis | Balanced pattern with telomerase reverse transcriptase to determine NSC proliferation and survival |
| TERRA2,23           | Postnatal mice brain | Neurogenesis | Upregulated in proliferating cerebellar neuronal progenitors |
| BC20090,262-264     | 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 |
| BC1262-265          | 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-AS266 | Mice brain, human brain neurons | Cognitive decline | Suppress protein synthesis (BDGF, GDNF, and EPHB2) involved in neurite elaboration |
| GOMAFU267           | Human brain | Cognitive decline | Instruct alternate splicing in synaptic plasticity |
| NEAT1268            | Mice brain | Cognitive decline | Modulate ion channel components |
| BACE1-AS186         | Human and Mice brain | Neurodegeneration | Modulate BACE1 expression and Aβ aggregation |
| SORL1-AS187         | Human brain | Neurodegeneration | Direct alternate splicing of SORL1 and Aβ formation |
| UCHL1-AS188,269,270 | Human brain | Neurodegeneration | Regulate UCHL1 expression, which facilitates pathogenic protein aggregation in AD and PD |
| LRPI-AS185,271      | Human brain | Neurodegeneration | Regulate LRPI expression and Aβ metabolism in AD |
| I7A157              | Human brain, cell line | Neurodegeneration | Induce alternate splicing of GABA protein isoform; Enhance Aβ secretion in AD |
| ANRIL189            | Human brain | Neurodegeneration | Regulate CDKN2B expression, which is accumulated in neurofibrillary tangles and amyloid plaques in AD |
| SNHG1191            | Mice brain, human cell line | Neurodegeneration | Promote α-synuclein in PD by targeting miR-15b-5p |
| G069488192          | Human cell line | Neurodegeneration | Regulate neurite regeneration and neural restoration by suppressing NEDD9 under α-synuclein accumulation in AD |
| RP11-142J21.2192   | Human cell line | Neurodegeneration | Promote apoptosis by suppressing SEMA6D via MAPK under α-synuclein accumulation in AD |
| NEAT1, MEG3, Rian, Mirg198 | Mice liver | Liver aging | Upregulated in healthy aging liver |
| H1960.67            | Mice cell line | Myogenesis | Modulate myoblast differentiation and muscle regeneration |
| IncMD1200,203       | Mice cell line | Myogenesis | Modulate myoblast differentiation during aging |
| SIRT1-AS206         | Mice cell line | Myogenesis | Modulate myoblast differentiation |
| MALAT1204,205       | Mice muscle, Mice and human cell | Myogenesis | Promote myoblast proliferation and differentiation in aging muscle |
| YY1209              | Mice cell line | Myogenesis | Upregulated in myoblasts but downregulated during differentiation; Regulate myogenesis at the transcriptional level |
| Glt2/Meg3210        | Mice cell line | Myogenesis | Maintain muscle development |
| MAR1208             | Mice cell line | Myogenesis | Attenuate muscle atrophy induced by aging |
| MALAT1212-216       | Human and mice cell | Angiogenesis, vascular remodeling | Control EC proliferation and senescence; mediate angiogenesis and vascular inflammation |
| MEG3217,218         | Mice vessel, human cell | Angiogenesis | Upregulated in senescent ECs; depletion of MEG3 promotes sprouting and EC proliferation |
| ANRIL219-223        | Human artery and cell | Atherosclerosis | Distinct modulation on VSMC proliferation and plaque formation according to different splicing variants |

(Continues)
and amyloid plaques in AD brain. Expression of BC200 was decreased in the normal aging brain, but elevated in AD brain. The accumulated pathological protein in PD brain is α-synuclein, contained in Lewy body. The identified genes involved in PD pathology include Parkin, PINK1, PARK7, 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.

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. 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. 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. A group of differentially expressed lncRNAs in mouse have been identified in the above pathophysioligies, including NEAT1, MEG3, Rian, and Mirg. Rian and MEG3 could regulate proliferation

### Table 1 (Continued)

| lncRNAs (References) | Samples studied | Processes | Effect during aging or other implications |
|----------------------|-----------------|----------|------------------------------------------|
| H19<sup>272-274</sup> | Rat artery, human cell | Atherosclerosis | Modulate EC and VSMC proliferation and homeostasis |
| ASncmRNA-2<sup>183</sup> | Mice cell | Vascular aging | Upregulated in aortas from aged mice and senescent ECs |
| HOTAIR<sup>225</sup> | Human artery, cell line | Atherosclerosis | Downregulated in ECs form atherosclerotic plaques; regulate EC proliferation and migration |
| MIA<sup>224</sup> | Rat, human cell | Angiogenesis | Regulate EC function |
| TUG1<sup>224-227</sup> | Rat and mouse cell | Atherosclerosis | Regulate EC apoptosis and VSMC homeostasis |
| linc-p21<sup>91,95,228</sup> | Mice cell | Atherosclerosis | Promote apoptosis and suppress proliferation in VSMCs and macrophages |
| Gas5<sup>229-231</sup> | Rat, human cell | Atherosclerosis, vascular remodeling | Promote VSMC proliferation and migration; guide macrophage polarization |
| HOXC-A<sup>2</sup>| Human artery | Atherosclerosis | Downregulated in atherosclerotic plaques through inflammatory responses |
| linc0005<sup>233</sup> | Human cell | Atherosclerosis | Promote monocyte activation and vascular inflammation |
| IncRNA OTTHUMT0000038702<sup>234</sup> | Human plasma and cell, | Atherosclerosis | Promote inflammation in macrophages |
| IncRNA RP5-833A20.1<sup>275</sup> | Mice artery and cell | Atherosclerosis | Regulated cholesterol homeostasis and inflammatory responses in foam cells |
| H19<sup>235</sup> | Human cell | Osteogenesis | Promote osteoblast differentiation |
| MALAT1<sup>236</sup> | Human cell | Osteogenesis | Induce osteogenic differentiation |
| HOTAIR<sup>237</sup> | Human cell | Osteogenesis | Suppress osteogenic differentiation |
| DANCER<sup>238</sup> | Human cell | Osteogenesis | Suppress osteogenic differentiation |
| MEG3<sup>239,240</sup> | Human cell | Osteogenesis | Suppress osteogenic differentiation |
| MIA<sup>241</sup> | Human cell | Osteogenesis | Suppress osteogenic differentiation under inflammation |
| MIR31HG<sup>242</sup> | Human cell | Osteogenesis | Rescue osteogenic differentiation inhibited by inflammation |
| DANCER<sup>238,243</sup> | Human bone and cell | Osteoporosis | Promote osteoblast differentiation; suppress osteogenic differentiation |
| H19<sup>107</sup> | Mice tissue | Lipid deposition | Imprint IGF2 and affect lipid deposition |
| PLUTO<sup>251</sup> | Human islets | T2DM | Regulate β-cell function and pancreatic formation |
| β-linc1<sup>252</sup> | Mice islets | T2DM | Associated with β-cell loss |
| HI-LNC901<sup>253</sup> | Human islets | T2DM | Correlated with insulin exocytosis |
| Kcnq1ot1, HI-LNC78, HI-LNC80<sup>254</sup> | Human islets | T2DM | Upregulated in T2DM Sense blood glucose level |
| HI-LNC45<sup>254</sup> | 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.
by directly recruiting PRC2.\(^{199}\) Mrg 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.\(^{50}\) 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 IncMD1 exerts as a decoy for miR-133 and miR-135, which is enhanced by HuR, to limit its impact on the expression of Elav1 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, Glt2Meg3, 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 cardiovasculardiseases (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 IncRNA in atherosclerosis is controversial, as different splicing variants of ANRIL might play distinct roles.\(^{219-223}\) Also, H19, ANcmRNA-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, IncRNAs including HOXC-AS, Gas5, linc00305, IncRNA OTTHUMT00000387022, and IncRNA RPS-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 conducive 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, DANCER, MEG3, MIAT, and MIR31HG) and osteoclast differentiation (eg, DANCER) via specific target miRNAs 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 miRNAs, recent strategies have applied the systematic analysis of IncRNAs-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_P428960544, 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. IncRNAs 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 Inc-RAP-n, which are specifically regulated during adipogenesis through PPARγ and CEBPα. However, the direct impacts of individual Inc-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.\textsuperscript{251} \(\beta\text{linc}1\), a \(\beta\)-cell long intergenic noncoding RNA, could modulate \(\beta\)-cell formation and function.\textsuperscript{252} \(HI\text{-LNC901}\) was reported to be directly correlated with insulin exocytosis.\textsuperscript{253} In addition, high levels of \(Kcnq1ot1\), \(HI\text{-LNC78}\), and \(HI\text{-LNC80}\) and low level of \(HI\text{-LNC45}\) were observed in pancreatic islets from diabetic individuals or in the presence of high glucose, indicating the function of sensing blood glucose levels.\textsuperscript{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.\textsuperscript{255} SASP-related IncRNAs 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 IncRNAs, such as \(\text{inc-MAF-4}\) and \(\text{mrmp}\), post-transcriptionally regulated CD4\(^+\)T-cell subsets, but no direct or indirect evidences point to their involvement in aging.\textsuperscript{256,257}

4 | CONCLUSION AND PERSPECTIVES

As concluding remarks, the emerging role of IncRNAs 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 IncRNAs 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 IncRNAs 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 IncRNAs 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 IncRNAs systematically. Although the potential usefulness of IncRNAs 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 IncRNAs in aging.

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CONFLICT OF INTEREST

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REFERENCES

1. Lopez-Otin C, Blasco MA, Partridge L, et al. The hallmarks of aging. Cell. 2013;153(6):1194-1217.
2. Larson KJ, Hamlin RJ, Sprung J, et al. Associations between Charlson Comorbidity Index and surgical risk severity and the surgical outcomes in advanced-age patients. Am Surg. 2014;80(6):555-560.
3. Divo MJ, Celli BR, Poblador-Blou B, et al. Chronic Obstructive Pulmonary Disease (COPD) as a disease of early aging: evidence from the EpiChron Cohort. PLoS ONE. 2018;13(2):e0193143.
4. Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1211-1259.
5. Dwolatzky T, Brodsky J, Azaia F, et al. Coming of age: health-care challenges of an ageing population in Israel. Lancet. 2017;389(10088):2542-2550.
6. Dieleman JL, Squires E, Bui AL, et al. Factors associated with increases in US health care spending, 1996–2013. JAMA. 2017;318(17):1668-1678.
7. Consortium EP, Birney E, Stamatoyannopoulos JA, et al. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature. 2007;447(7146):799-816.
8. Consortium EP. An integrated encyclopedia of DNA elements in the human genome. Nature. 2012;489(7414):57-74.
9. Kung JT, Colognori D, Lee JT. Long noncoding RNAs: past, present, and future. Genetics. 2013;193(3):651-669.
10. St Laurent G, Wahlestedt C, Karanpov P. The Landscape of long noncoding RNA classification. Trends Genet. 2015;31(5):239-251.
11. Elling R, Chan J, Fitzgerald KA. Emerging role of long noncoding RNAs as regulators of innate immune cell development and inflammatory gene expression. Eur J Immunol. 2016;46(3):504-512.
12. Degirmenci U, Lei S. Role of IncRNAs in cellular aging. Front Endocrinol (Lausanne). 2016;7:151.
13. Guttmann M, Donaghey J, Carey BW, et al. lincRNAs act in the circuitry controlling pluripotency and differentiation. Nature. 2011;477(7364):295-300.
14. Loewer S, Cabili MN, Guttmann M, et al. Large intergenic non-coding RNA-RoR modulates reprogramming of human induced pluripotent stem cells. Nat Genet. 2010;42(12):1113-1117.
15. McHugh CA, Chen CK, Chow A, et al. The Xist IncRNA interacts directly with SHARP to silence transcription through HDAC3. Nature. 2015;521(7511):232-236.
16. Mercer TR, Mattick JS. Structure and function of long noncoding RNAs in epigenetic regulation. Nat Struct Mol Biol. 2013;20(3):300-307.
17. Rossi MN, Antonangeli F. LncRNAs: new players in apoptosis control. Int J Cell Biol. 2014;2014:473857.
18. Lazarides S, Vallot C, Briois S, et al. A vlincRNA participates in senescence maintenance by relieving H2A.Z-mediated repression at the INK4 locus. Nat Commun. 2015;6:5971.
19. Grammatikakis I, Panda AC, Abdelmohsen K, et al. Long noncoding RNAs (lncRNAs) and the molecular hallmarks of aging. Aging (Albany NY). 2014;6(12):992-1009.
20. Greco S, Gorospe M, Martelli F. Noncoding RNA in age-related cardiovascular diseases. J Mol Cell Cardiol. 2015;83:142-155.
21. Ben-Porath I, Weinberg RA. The signals and pathways activating cellular senescence. Int J Biochem Cell Biol. 2005;37(5):961-976.
22. Hernandez-Segura A, Nehme J, Demaria M. Hallmarks of cellular senescence. Trends Cell Biol. 2018;28(6):436-453.
23. Frenk S, Houseley J. Gene expression hallmarks of cellular ageing. Biochim Biophys Acta. 2018;Suppl 1:1-20.
24. Aravintan A. Cellular senescence: a hitchhiker's guide. Hum Cell. 2015;28(2):51-64.
25. Abdelmohsen K, Gorospe M. Noncoding RNA control of cellular senescence. Wiley Interdiscip Rev RNA. 2015;6(6):615-629.
26. Tripathi 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;9(3):e1003368.
27. Dong Y, Liang G, Yuan B, et al. MALAT1 promotes the proliferation and metastasis of osteosarcoma cells by activating the PI3K/Akt pathway. Tumour Biol. 2015;36(3):1477-1486.
28. Hu L, Wu Y, Tan D, et al. Up-regulation of long noncoding RNA MALAT1 contributes to proliferation and metastasis in esophageal squamous cell carcinoma. J Exp Clin Cancer Res. 2015;34:7.
29. Yang MH, Hu ZY, Xu C, et al. MALAT1 promotes colorectal cancer cell proliferation/migration/invasion via PRKA kinase anchor protein 9. Biochim Biophys Acta. 2015;1852(1):166-174.
30. Guo F, Li Y, Liu Y, et al. Inhibition of metastasis-associated lung adenocarcinoma transcript 1 in CaSkii human cervical cancer cells suppresses cell proliferation and invasion. Acta Biochim Biophys Sin (Shanghai). 2010;42(3):224-229.
31. Zhao Z, Chen C, Liu Y, et al. 17beta-Estradiol treatment inhibits breast cell proliferation, migration and invasion by decreasing MALAT-1 RNA level. Biochem Biophys Res Commun. 2014;445(2):388-393.
32. Eisemann M, Gutschner T, Hammerle M, et al. Loss of the abundant nuclear non-coding RNA MALAT1 is compatible with life and development. RNA Biol. 2012;9(8):1076-1087.
33. Nakagawa S, Ip JY, Shioi G, et al. Malat1 is not an essential component of nuclear speckles in mice. RNA. 2012;18(8):1487-1499.
34. Zhang B, Arun G, Mao YS, et al. The IncRNA Malat1 is dispensable for mouse development but its transcription plays a cis-regulatory role in the adult. Cell Rep. 2012;2(1):111-123.
35. Pasman E, Laurendeu I, Heron D, et al. Characterization of a germ-line deletion, including the entire INK4/ARF locus, in a melanoma-neural system tumor family: identification of ANRIL, an antisense noncoding RNA whose expression co-clusters with ARF. Cancer Res. 2007;67(8):3963-3969.
36. Kotake Y, Nakagawa T, Kitagawa K, et al. Long non-coding RNA ANRIL is required for the PRC2 recruitment to and silencing of p15 INK4B tumor suppressor gene. Oncogene. 2011;30(47):4750-4756.
37. Zhang X, Zhou Y, Mehta KR, et al. A pituitary-derived MEG3 isoform functions as a growth suppressor in tumor cells. J Clin Endocrinol Metab. 2003;88(11):5119-5126.
38. Lu KH, Li W, Liu XH, et al. Long non-coding RNA MEG3 inhibits NSCLC cell proliferation and induces apoptosis by affecting p53 expression. BMC Cancer. 2013;13:461.
39. He Y, Luo Y, Liang B, et al. Potential applications of MEG3 in cancer diagnosis and prognosis. Oncotarget. 2017;8(42):73282-73295.
40. Zhou Y, Zhong Y, Wang Y, et al. Activation of p53 by MEG3 non-coding RNA. J Biol Chem. 2007;282(24):24731-24742.
41. Ying L, Huang Y, Chen H, et al. Downregulated MEG3 activates autophagy and increases cell proliferation in bladder cancer. Mol BioSyst. 2013;9(3):407-411.
42. Anwar SL, Krech T, Hasemeier B, et al. Loss of imprinting and allelic switching at the DLK1-MEG3 locus in human hepatocellular carcinoma. PLoS ONE. 2012;7(11):e49462.
43. Qin R, Chen Z, Ding Y, et al. Long non-coding RNA MEG3 inhibits the proliferation of cervical carcinoma cells through the induction of cell cycle arrest and apoptosis. Neoplasma. 2013;60(5):486-492.
44. Johnson R. Long non-coding RNAs in Huntington's disease neurodegeneration. Neurobiol Dis. 2012;46(2):245-254.
45. Thorvaldsen JL, Duran KL, Bartolomei MS. Deletion of the H19 differentially methylated domain results in loss of imprinting expression of H19 and Igf2. Genes Dev. 1998;12(23):3693-3702.
46. Kallen AN, Zhou XB, Xu J, et al. The imprinted H19 IncRNA antagonizes let-7 microRNAs. Mol Cell. 2013;52(1):101-112.
47. Zhu M, Chen Q, Liu X, et al. IncRNA H19/mir-675 axis represses prostate cancer metastasis by targeting TGFB1. FEBS J. 2014;281(8):3766-3775.
48. Li H, Yu B, Li J, et al. Overexpression of IncRNA H19 enhances carcinoma metastasis and repression of gastric cancer. Oncotarget. 2014;5(8):2318-2329.
49. Sun H, Wang G, Peng Y, et al. H19 IncRNA mediates 17beta-estradiol-induced cell proliferation in MCF-7 breast cancer cells. Oncol Rep. 2015;33(6):3045-3052.
50. Ratajczak MZ. Igf2-H19, an implanted tandem gene, is an important regulator of embryonic development, a guardian of proliferation of adult pluripotent stem cells, a regulator of longevity, and a ‘passkey’ to carcinogenesis. Folia Histochem Cytobiol. 2012;50(2):171-179.
51. Fu VX, Dobosy JR, Desotelte JA, et al. Aging and cancer-related loss of insulin-like growth factor 2 imprinting in the mouse and human prostate. Cancer Res. 2008;68(16):6797-6802.
66. Jones BK, Levorse J, Tilghman SM. Deletion of a nuclease-sensitive region between the Igf2 and H19 genes leads to Igf2 misregulation and increased adiposity. *Hum Mol Genet*. 2001;10(8):807-814.

67. Dey BK, Pfeifer K, Dutta A. The H19 long noncoding RNA gives rise to microRNAs miR-675-3p and miR-675-5p to promote skeletal muscle differentiation and regeneration. *Genes Dev*. 2014;28(5):491-501.

68. Wang XS, Zhang Z, Wang HC, et al. Rapid identification of UCA1 as a very sensitive and specific unique marker for human bladder carcinoma. *Clin Cancer Res*. 2006;12(16):4851-4858.

69. Wang H, Guan Z, He K, et al. LncRNA UCA1 in anti-cancer drug resistance. *Oncotarget*. 2017;8(38):64638-64650.

70. Kumar PP, Emechebe U, Smith R, et al. Coordinated control of senescence by IncRNA and a novel T-box3 co-repressor complex. *Elife*. 2014;3:e02805.

71. Xue M, Chen W, Li X. Urothelial cancer associated 1: a long non-coding RNA with a crucial role in cancer. *J Cancer Res Clin Oncol*. 2016;142(7):1407-1419.

72. Hu X, Feng Y, Zhang D, et al. A functional genomic approach identifies FAI1 as an oncogenic long noncoding RNA that associates with BMI1 and represses p21 expression in cancer. *Cancer Cell*. 2014;26(3):344-357.

73. Zhong X, Hu X, Zhang L. Oncogenic long noncoding RNA FAI1 in human cancer. *Mol Cell Oncol*. 2015;2(2):e977154.

74. Hollander MC, Alamo I, Fornace AJ Jr. A novel DNA damage-inducible transcript, gadd7, inhibits cell growth, but lacks a protein product. *Nucleic Acids Res*. 1996;24(9):1589-1593.

75. Liu X, Li D, Zhang W, et al. Long non-coding RNA gadd7 interacts with TDP-43 and regulates Cdk6 mRNA decay. *EMBO J*. 2012;31(23):4415-4427.

76. Rader J, Russell MR, Hart LS, et al. Dual CDK4/CDK6 inhibition induces cell-cycle arrest and senescence in neuroblastoma. *Clin Cancer Res*. 2013;19(22):6173-6182.

77. Augoff K, McCue B, Plow EF, et al. miR-31 and its host gene IncRNA LOC554202 are regulated by promoter hypermethylation in triple-negative breast cancer. *Mol Cancer*. 2012;11:5.

78. Dellago H, Preschitz-Kammerhofer B, Terlecki-Zaniewicz L, et al. High levels of oncomiR-21 contribute to the senescence-induced growth arrest in normal human cells and its knock-down increases the replicative lifespan. *Aging Cell*. 2013;12(3):446-458.

79. Xi S, Yang M, Tao Y, et al. Cigarette smoke induces C/EBP-beta-mediated activation of miR-31 in normal human respiratory epithelia and lung cancer cells. *PLoS ONE*. 2010;5(10):e13764.

80. Shih JW, Chiang WF, Wu ATH, et al. Long non-coding RNA LncHIFCAR/MIR31HG is a HIF-1alpha co-activator driving oral cancer proliferation, functional diversification and neurodegenerative disease. *Front Neurol*. 2015;6:45.

81. Liu Z, Bai J, Zhang L, et al. Conditional knockout of microRNA-31 promotes the development of colitis associated cancer. *Biochem Biophys Res Commun*. 2017;479(1):62-68.

82. Qin J, Ning H, Zhou Y, et al. LncRNA MIR31HG overexpression serves as a poor prognostic biomarker and promotes cells proliferation in lung adenocarcinoma. *Biomed Pharmacother*. 2018;99:363-368.

83. Montes M, Nielsen MM, Maglieri G, et al. The IncRNA MIR31HG regulates p16(INK4A) expression to modulate senescence. *Nat Commun*. 2015;6:6967.

84. Di Agostino S, Strano S, Emiliozzi V, et al. Gain of function of mutant p53: the mutant p53/NF-Y protein complex reveals an aberrant transcriptional mechanism of cell cycle regulation. *Cancer Cell*. 2006;10(3):191-202.

85. Hung T, Wang Y, Lin MF, et al. Extensive and coordinated transcription of noncoding RNAs within cell-cycle promoters. *Nat Genet*. 2011;43(7):621-629.

86. Matsuoka K, Chen KY. Possible role of subunit A of nuclear factor Y (NF-YA) in normal human diploid fibroblasts during senescence. *Biogerontology*. 2000;1(3):261-271.

87. Wang Y, Zhang M, Xu H, et al. Discovery and validation of the tumor-suppressive function of long noncoding RNA PANDA in human diffuse large B-cell lymphoma through the inactivation of MAPK/ERK signaling pathway. *Oncotarget*. 2017;8(42):72182-72196.

88. Puvvula PK, Desetty RD, Pineau P, et al. Long noncoding RNA PANDA and scaffold-attachment-factor SAFA control senescence entry and exit. *Nat Commun*. 2014;5:5323.

89. Huarte M, Guttman M, Feldser D, et al. A large intergenic noncoding RNA induced by p53 mediates global gene repression in the p53 response. *Cell*. 2010;142(3):409-419.

90. Dimitrova N, Zamudio JR, Jong RM, et al. LincRNA-p21 activates p21 in cis to promote Polycomb target gene expression and to enforce the G1/S checkpoint. *Mol Cell*. 2014;54(5):777-790.

91. Wu G, Cai J, Han Y, et al. LincRNA-p21 regulates neo-intima formation, vascular smooth muscle cell proliferation, apoptosis, and atherosclerosis by enhanced p53 activity. *Circulation*. 2014;130(17):1452-1465.

92. Yoon JH, Abdelmohsen K, Srikantan S, et al. LncRNA-p21 suppresses target mRNA translation. *Mol Cell*. 2012;47(4):648-655.

93. Bao X, Wu H, Zhu X, et al. The p53-induced lincRNA-p21 derailed somatic cell reprogramming by sustaining H3K9me3 and Cpg methylation at pluripotency gene promoters. *Cell Res*. 2015;25(1):80-92.

94. Cekin N, Ozcan A, Goksel S, et al. Decreased FENDRR and LincRNA-p21 expression in atherosclerotic plaque. *Anat J Cardiol*. 2018;19(2):131-136.

95. Tang SS, Cheng J, Cai MY, et al. Association of lincRNA-p21 haplotype with coronary artery disease in a Chinese Han population. *Dis Markers*. 2016;2016:9109743.

96. Tang SS, Zheng BY, Xiong XD. LincRNA-p21: implications in human diseases. *Int J Mol Sci*. 2015;16(8):18732-18740.

97. Marin-Bejar O, Marchese FP, Athie A, et al. Pint lincRNA connects nuclear factor of activated T cells with known genes in the polycomb complex. *2015;6:655.

98. Li Z, Shen J, Chan MT, et al. TUG1, a pivotal oncogenic long non-coding RNA of human cancers. *Cell Prolif*. 2016;49(4):471-475.

99. Khalil AM, Guttman M, Hurae M, et al. Many human large intergenic noncoding RNAs associate with chromatin-modifying complexes and affect gene expression. *Proc Natl Acad Sci USA*. 2009;106(28):11667-11672.

100. Lin YH, Wu MH, Huang YH, et al. Taurine up-regulated gene 1 functions as a master regulator to coordinate glycolysis and metabolism in hepatocellular carcinoma. *Hepatology*. 2014;61(1):188-203.

101. Barry G, Guennewig B, Fung S, et al. Long non-coding RNAs in ischemic stroke. *Cell Death Dis*. 2018;9(3):281.

102. Wu P, Zuo X, Deng H, et al. Roles of long noncoding RNAs in brain development, functional diversification and neurodegenerative diseases. *Brain Res Bull*. 2013;97:69-80.

103. Chen J, Jia YS, Liu GZ, et al. Role of LncRNA TUG1 in intervertebral disc degeneration and nucleus pulposus cells via regulating Wnt/beta-catenin signaling pathway. *Biochem Biophys Res Commun*. 2017;491(3):668-674.

104. Li G, Song H, Chen L, et al. TUG1 promotes lens epithelial cell apoptosis by regulating miR-421/caspase-3 axis in age-related cataract. *Exp Cell Res*. 2017;356(1):20-27.

105. Young TL, Matsuda T, Cepko CL. The noncoding RNA taurine upregulated gene 1 is required for differentiation of the murine retina. *Curr Biol*. 2005;15(6):501-512.

106. Panzitt K, Tschernatsch MM, Guelly C, et al. Characterization of HULC, a novel gene with striking up-regulation in hepatocellular carcinoma, as nondcoding RNA. *Gastroenterology*. 2007;132(1):330-342.
108. Yang F, Zhang L, Huo XS, et al. Long noncoding RNA high expression in hepatocellular carcinoma facilitates tumor growth through enhancer of zeste homolog 2 in humans. *Hepatology*, 2011;54(5):1679-1689.

109. Du Y, Kong G, You X, et al. Elevation of highly up-regulated in liver cancer (HULC) by hepatitis B virus X protein promotes hepatoma cell proliferation via down-regulating p18. *J Biol Chem*. 2012;287(31):26302-26311.

110. Zou Y, Li J, Chen Y, et al. BANCR: a novel oncogenic long non-coding RNA in human cancers. *Oncotarget*. 2017;8(55):94997-95004.

111. Yu TY, Kao YW, Lin JJ. Telomeric transcripts stimulate telomere recombination to suppress senescence in cells lacking telomerase. *Proc Natl Acad Sci USA*. 2014;111(9):3377-3382.

112. Chen R, Zhang K, Chen H, et al. Telomeric deficiency causes alveolar stem cell senescence-associated low-grade inflammation in lungs. *J Biol Chem*. 2015;290(52):30813-30829.

113. Saeed H, Qiü W, Li C, et al. Telomerase activity promotes osteoblast differentiation by modulating IGF-signaling pathway. *Bioconjugate Chemistry*. 2015;16(6):733-745.

114. Ghosh A, Saginc G, Leow SC, et al. Telomerase directly regulates NF-kappaB-dependent transcription. *Nat Cell Biol*. 2012;14(12):1270-1281.

115. Samper E, Flores JM, Blasco MA. Restoration of telomerase activity rescues chromosomal instability and premature aging in Terc−/− mice with short telomeres. *EMBO Rep*. 2001;2(9):800-807.

116. Li S, Crothers J, Haqq CM, et al. Somatic and gene expression responses involved in the rapid growth inhibition of human cancer cells by RNA interference-mediated depletion of telomerase RNA. *J Biol Chem*. 2005;280(25):23709-23717.

117. Luke B, Panza A, Redon S, et al. The Rat1p 5′-3′ exonuclease degrades telomeric repeat-containing RNA and promotes telomere elongation in *Saccharomyces cerevisiae*. *Mol Cell*. 2008;32(4):465-477.

118. Misino S, Bonetti D, Luke-Glaser S, et al. Increased TERRA levels and RNase H sensitivity are conserved hallmarks of post-cancerous cell proliferation via down-regulation of TERRA: aging and cancer. *Proc Natl Acad Sci USA*. 2013;110(25):12051-12056.

119. Penny GD, Kay GF, Sheardown SA, et al. Requirement for Xist in X chromosome inactivation. *Nature*. 1996;379(6561):131-137.

120. Fukuoka A, Tomikawa J, Miura T, et al. The role of maternal-specific H3K9me3 modification in establishing imprinted X-chromosome inactivation and embryogenesis in mice. *Nat Commun*. 2014;5:5464.

121. Abdelmohsen K, Panda A, Kang MJ, et al. Senescence-associated IncRNAs: senescence-associated long non-coding RNAs. *Aging Cell*. 2013;12(5):890-900.

122. Du M, Zhou W, Beatty LG, et al. The KCNQ1OT1 promoter, a key regulator of genomic imprinting in human chromosome 11p15.5. *Genomics*. 2004;84(2):288-300.

123. Kanduri C. Functional insights into long antisense noncoding RNA Kcnq1ot1 mediated bidirectional silencing. *RNA Biol*. 2008;5(4):208-211.

124. Mohammad F, Mondal T, Guseva N, et al. Kcnq1ot1 noncoding RNA mediates transcriptional gene silencing by interacting with Dnmt1. *Development*. 2010;137(15):2493-2499.

125. Travers ME, Mackay DJ, Dekker Nittert M, et al. Insights into the molecular mechanism for type 2 diabetes susceptibility at the KCNQ1 locus from temporal changes in imprinting status in human islets. *Diabetes*. 2013;62(3):987-992.

126. Han J, Huang M, Zhao H, et al. A novel tetranucleotide repeat polymorphism within KCNQ1OT1 confers risk for hepatocellular carcinoma. *DNA Cell Biol*. 2013;32(11):628-634.

127. Arslan S, Berkan O, Lalem T, et al. Long non-coding RNAs in the atherosclerotic plaque. *Atherosclerosis*. 2017;266:176-181.

128. Vaalsto M, Wagner DR, Devaux Y. Long non-coding RNAs in patients with acute myocardial infarction. *Circ Res*. 2014;115(7):668-677.

129. Beckedorff FC, Ayupe AC, Crocci-Souza R, et al. The intronic long noncoding RNA ANRASSF1 recruits PRC2 to the RASSF1A promoter, reducing the expression of RASSF1A and increasing cell proliferation. *PLoS Genet*. 2013;9(8):e1003705.

130. Damaschke NA, Yang B, Bhsari S, et al. Epigenetic susceptibility factors for prostate cancer with aging. *Prostate*. 2013;73(16):1721-1730.

131. Nishida N, Nagasaka T, Nishimura T, et al. Aberrant methylation of multiple tumor suppressor genes in aging liver, chronic hepatitis, and hepatocellular carcinoma. *Hepatology*. 2008;47(3):908-918.

132. Strunnikova M, Schagdarsurengin U, Kehlen A, et al. Chromatin inactivation precedes de novo DNA methylation during the progressive epigenetic silencing of the RASSF1A promoter. *Mol Cell Biol*. 2005;25(10):3923-3933.

133. Nagano T, Mitchell JA, Sanz LA, et al. The Air noncoding RNA epigenetically silences transcription by targeting G9a to chromatin. *Science*. 2008;322(5908):1717-1720.

134. Santoro F, Mayer D, Klement RM, et al. Imprinted Igf2r silencing depends on continuous Airm IncRNA expression and is not restricted to a developmental window. *Development*. 2013;140(6):1184-1195.

135. Xu W, Zhang ZX, Yang JP, et al. [The profile of IgF2r gene expression and H3 histone modifications in replicative cell senescence]. *Sichuan Da Xue Xue Bao Yi Xue Ban*. 2014;45(1):6-9.

136. Abdul Rahman A, Abdul Karim N, Abdul Hamid NA, et al. Senescence-related changes in gene expression of peripheral blood mononuclear cells from octo/nonagenarians compared to their offspring. *Oxid Med Cell Longev*. 2013;2013:189129.

137. Di Ruscio A, Ebralidze AK, Benoukraf T, et al. DNMT1-interacting RNAs block gene-specific DNA methylation. *Nature*. 2013;503(7476):371-376.
148. Wang H, Iakova P, Wilde M, et al. C/EBPalpha arrests cell proliferation through direct inhibition of Cdk2 and Cdk4. Mol Cell. 2001;8(4):817-828.

149. Hong IH, Lewis K, Iakova P, et al. Age-associated change of C/EBP family proteins causes severe liver injury and acceleration of liver proliferation after CCI4 treatments. J Biol Chem. 2014;289(2):1106-1118.

150. Karagianidou I, Tchkonia T, Dobson DE, et al. Altered expression of C/EBP family members results in decreased adipogenesis with aging. Am J Physiol Regul Integr Comp Physiol. 2001;280(6):R1772-R1780.

151. Huggins CJ, Malik R, Lee S, et al. C/EBPgamma suppresses senescence and inflammatory gene expression by heterodimerizing with C/EBPbeta. Mol Cell Biol. 2013;33(16):3242-3258.

152. Schmitz KM, Mayer C, Postepska A, et al. Interaction of noncoding RNA with the rDNA promoter mediates recruitment of DNMT3b and silencing of rRNA genes. Genes Dev. 2010;24(20):2264-2269.

153. Johnson R, Strehler BL. Loss of genes coding for ribosomal RNA in the aging brain cells. Nature. 1972;240(5381):412-414.

154. Pietrzak M, Rempala G, Nelson PT, et al. Epigenetic silencing of nucleolar rRNA genes in Alzheimer's disease. PLoS ONE. 2011;6(7):e22585.

155. Machwe A, Orren DK, Bohr VA. Accelerated methylation of ribosomal RNA genes during the cellular senescence of Werner syndrome fibroblasts. FASEB J. 2000;14(12):1715-1724.

156. Alemany R, Perona JS, Sanchez-Dominguez JM, et al. G protein-coupled receptor systems and their lipid environment in health disorders during aging. Biochim Biophys Acta. 2007;1768(4):964-975.

157. Massone S, Vassallo I, Fiorino G, et al. 17a, a novel non-coding RNA, regulates GABA B alternative splicing and signaling in response to inflammatory stimuli and in Alzheimer disease. Neurobiol Dis. 2011;41(2):308-317.

158. Nakagawa S, Hirano T. Gathering around Fire. Nat Struct Mol Biol. 2014;21(3):207-208.

159. Lu Y, Liu X, Xie M, et al. The NF-kappaB-responsive long noncoding RNA FIRE regulates posttranscriptional regulation of inflammatory gene expression through interacting with hnrRNP J. Immunol. 2017;199(10):3571-3582.

160. Cui H, Xie N, Tan Z, et al. The human long noncoding RNA IncIL7R regulates the inflammatory response. Eur J Immunol. 2014;44(7):2085-2095.

161. Yang F, Huo XS, Yuan SX, et al. Repression of the long non-coding RNA NEAT1-dependent SFPQ relocation from promoter region to paraspeckle mediates IL8 expression upon immune stimuli. Mol Cell. 2014;53(3):393-406.

162. Chen Y, Qiu J, Chen B, et al. Long non-coding RNA NEAT1 plays an important role in sepsis-induced acute kidney injury by targeting miR-204 and modulating the NF-kappaB pathway. Int Immunopharmacol. 2018;59:252-260.

163. Zhang F, Wu L, Qian J, et al. Identification of the long noncoding RNA NEAT1 as a novel inflammatory regulator acting through MAPK pathway in human lupus. J Autoimmun. 2016;75:96-104.

164. Huang-Fu N, Cheng JS, Wang Y, et al. Neat1 regulates oxidized low-density lipoprotein-induced inflammation and lipid uptake in macrophages via paraspeckle formation. Mol Med Rep. 2018;17(2):3092-3098.

165. Wang Q, Wang W, Zhang F, et al. Neat1/miR-181c regulates Osteopontin (OPN)-mediated synoviocyte proliferation in osteoarthritis. J Cell Biochem. 2017;118(11):3775-3784.

166. Krawczyk M, Emerson BM. P50-associated COX-2 extragenic RNA (PACER) activates COX-2 gene expression by occluding repressive NF-kappaB complexes. Elife. 2014;3:e01776.

167. Pearson MJ, Philip AM, Heward JA, et al. Long intergenic noncoding RNAs mediate the human chondrocyte inflammatory response and are differentially expressed in osteoarthritic cartilage. Arthritis Rheumatol. 2016;68(4):845-856.

168. Li Z, Chao TC, Chang KY, et al. The long noncoding RNA THRIL regulates TNFalpha expression through its interaction with hnrRNPL. Proc Natl Acad Sci USA. 2014;111(3):1002-1007.

169. Rinn JL, Kertesz M, Wang JK, et al. Functional demarcation of extragenic RNA clusters. Nature. 2010;463(7285):1074-1079.

170. Somarowthu S, Legiewicz M, Chillon I, et al. HOTAIR forms an intricate and modular secondary structure. Mol Cell. 2015;58(2):353-361.

171. Zhang K, Sun X, Zhou C, et al. Long non-coding RNA HOTAIR promotes glioblastoma cell cycle progression in an EZH2 dependent manner. Oncotarget. 2015;6(11):537-546.

172. Ozes AR, Miller DF, Ozes ON, et al. NF-kappaB-HOTAIR axis links DNA damage response, chemoresistance and cellular senescence in ovarian cancer. Oncogene. 2016;35(41):5350-5361.

173. Yoon JH, Abdelmohsen K, Kim J, et al. Scaffold function of long non-coding RNA HOTAIR in protein ubiquitination. Nat Commun. 2013;4:2939.

174. Lauri A, Pompilio G, Capogrossi MC. The mitochondrial genome in aging and senescence. Ageing Res Rev. 2014;13:18-15.

175. Bianchessi V, Badi I, Bertolotti M, et al. The mitochondrial long noncoding RNA NEAT1 plays a role in the aging and senescence-phenotype. Aging (Albany NY). 2012;4(10):695-708.

176. Carpenter S, Aiello D, Atianand MK, et al. A long noncoding RNA regulates both activation and repression of immune response genes. Science. 2013;341(6147):789-792.

177. Hu G, Gong AY, Wang Y, et al. LinRNA-Cox2 promotes late inflammatory gene transcription in macrophages through modulating SWI/SNF-mediated chromatin remodeling. J Immunol. 2016;196(6):2799-2808.

178. Rapicavoli NA, Qu K, Zhang J, et al. A mammalian pseudogene IncRNA at the interface of inflammation and anti-inflammatory therapeutics. Elife. 2013;2:e00762.

179. Adler AS, Sinha S, Kawahara TL, et al. Motif module map reveals new functional roles of long noncoding RNA FTO in obesity and metabolic disease. Genome Biol. 2014;15(2):324-3257.

180. Clemson CM, Hutchison JN, Sara SA, et al. An architectural role for a nuclear noncoding RNA: NEAT1 RNA is essential for the structure of paraspeckles. Mol Cell. 2009;33(6):717-726.

181. Naganuma T, Hirose T. Paraspeckle formation during the biogenesis of long non-coding RNAs. RNA Biol. 2013;10(3):455-461.
189. Pereira Fernandes D, Bitar M, Jacobs FMJ, et al. Long non-coding RNAs in neuronal aging. Noncoding RNA. 2018;4(2):12.

190. Mus E, Hof PR, Tiedge H. Dendritic BC200 RNA in aging and in Alzheimer’s disease. Proc Natl Acad Sci USA. 2007;104(25):10679-10684.

191. Chen Y, Lian YJ, Ma YQ, et al. LncRNA SNHG1 promotes alpha-astrocyte nuclei in aging and in Alzheimer’s disease. Proc Natl Acad Sci USA. 2017;114(9):1389-1397.

192. Lin D, Liang Y, Jing X, et al. Microarray analysis of an synthetic alpha-synuclein induced cellular model reveals the expression profile of long non-coding RNA in Parkinson’s disease. Brain Res. 2018;1678:384-396.

193. Schmucker DL. Age-related changes in liver structure and function: implications for disease? Exp Gerontol. 2005;40(8-9):650-659.

194. Wynne HA, Cope LH, Mutch E, et al. The effect of age upon liver volume and apparent liver blood flow in healthy man. Hepatology. 1989;9(2):297-301.

195. Jung T, Bader N, Grune T. Lipofuscin: formation, distribution, and metabolic consequences. Ann N Y Acad Sci. 1989;9(2):297-304.

196. Wang Y, Pang WJ, Wei N, et al. Identification, stability and expression of Sirt1 antisense long noncoding RNA. EMBO J. 2015;34(26):30235-30243.

197. Kim IH, Kisseleva T, Brenner DA. Aging and liver disease. Ann N Y Acad Sci. 2005;104(4):1225-1234.

198. Boon RA, Hofmann P, Michalik KM, et al. Long noncoding RNA MEG3 controls endothelial cell aging and functioning: implications for regenerative angiogenesis. J Am Coll Cardiol. 2016;68(23):2589-2591.

199. He C, Yang W, Yang J, et al. Long noncoding RNA MEG3 negatively regulates proliferation and angiogenesis in vascular endothelial cells. DNA Cell Biol. 2017;36(6):475-481.

200. Holdt LM, Stahlinger A, Soss K, et al. Circular non-coding RNA ANRIL modulates ribosomal RNA maturation and atherosclerosis in humans. Nat Commun. 2016;7:12429.

201. Wang G, Mathur R, Hu X, et al. Long non-coding RNA ANRIL (CDKN2B-AS) is induced by the ATM-E2F1 signaling pathway. Cell Signal. 2013;25(5):1086-1095.

202. Congrains A, Kamide K, Katsuya T, et al. CVD-associated non-coding RNA, ANRIL, modulates expression of atherogenic pathways in VSMC. Biochim Biophys Acta. 2012;1819(4):612-616.

203. Holdt LM, Beutner F, Scholz M, et al. ANRIL expression is associated with atherosclerosis risk at chromosome 9p21. Arterioscler Thromb Vasc Biol. 2010;30(3):620-627.

204. Kojima K, Shinoda H, Tsuchida Y, et al. Functional analysis of the 9p21.3 coronary artery disease risk locus. Circ Res. 2017;120(10):1671-1677.

205. Yan B, Yao J, Liu JY, et al. IncRNA-MIAT regulates microvascular dysfunction by functioning as a competing endogenous RNA. Circ Res. 2015;116(7):1143-1156.

206. Peng Y, Meng K, Jiang L, et al. Thymic stromal lymphopoietin-induced HOTAIR activation promotes endothelial cell proliferation and migration in atherosclerosis. Biosci Rep. 2017;37(4):B5R20170351.

207. Chen C, Cheng G, Yang X, et al. Tanshinol suppresses endothelial cells apoptosis in mice with atherosclerosis via IncRNA TUG1 upregulating the expression of miR-26a. Am J Transl Res. 2016;8(7):2981-2991.

208. Chen R, Kong P, Zhang F, et al. EZH2-mediated alpha-actin methylation needs IncRNA TUG1, and promotes the cortex cytoskeleton formation in VSMCs. Gene. 2017;616:52-57.

209. He C, Ding JW, Li S, et al. The role of long intergenic noncoding RNA p21 in vascular endothelial cells. DNA Cell Biol. 2015;34(11):677-683.

210. Chen L, Yang W, Guo Y, et al. Exosomal IncRNA GAS5 regulates the apoptosis of macrophages and vascular endothelial cells in atherosclerosis. PLoS ONE. 2017;12(9):e0185406.

211. Ito I, Asai A, Suzuki S, et al. Mi2b macrophage polarization accompanied with reduction of long noncoding RNA GAS5. Biochem Biophys Res Commun. 2017;493(1):170-175.
Huang C, Hu YW, Zhao JJ, et al. Long noncoding RNA HOXC237. Wei B, Wei W, Zhao B, et al. Long non
Huang W, Thomas B, Flynn RA, et al. DDX5 and its associated lncRNA Rmrp modulate TH1 cell effector functions. Nature. 2015;528(7583):517-522.

3. Xiao X, Zhou T, Guo S, et al. LncRNA MALAT1 sponges miR-204 to promote osteoblast differentiation of human aortic valve interstitial cells through up-regulating Smad4. Int J Cardiol. 2017;243:404-412.

4. Wei B, Wei W, Zhao B, et al. Long non-coding RNA HOXAT inhibits miR-17-5p to regulate osteogenic differentiation and proliferation in non-traumatic osteonecrosis of femoral head. PLoS ONE. 2017;12(2):e0169079.

5. Jia Q, Jiang W, Ni L. Down-regulated non-coding RNA (lncRNA-ANCR) promotes osteogenic differentiation of periodontal ligament stem cells. Arch Oral Biol. 2015;60(2):234-241.

6. Li Z, Jin C, Chen S, et al. Long non-coding RNA MEG3 inhibits adipogenesis and promotes osteogenesis of human adipose-derived mesenchymal stem cells via miR-140-5p. Mol Cell Biochem. 2017;433(1-2):51-60.

7. Wang Q, Li Y, Zhang Y, et al. LncRNA MEG3 inhibited osteogenic differentiation of bone marrow mesenchymal stem cells from postmenopausal osteoporosis by targeting miR-133a-3p. Blended Pharmacother. 2017;89:1178-1186.

8. Jin C, Zheng Y, Huang Y, et al. Long non-coding RNA MIAT knockdown promotes osteogenic differentiation of human adipose-derived stem cells. Cell Biol Int. 2017;41(1):33-41.

9. Jin C, Jia L, Huang Y, et al. Inhibition of lncRNA MIR31HG promotes osteogenic differentiation of human adipose-derived stem cells. Stem Cells. 2016;34(11):2707-2720.

10. Tong X, Gu PC, Xu SZ, et al. Long non-coding RNA-DNCR in human circulating monocytes: a potential biomarker associated with postmenopausal osteoporosis. Biosci Biotechnol Biochem. 2015;79(5):732-737.

11. Clark MB, Johnston RL, Inostroza-Ponta M, et al. Genome-wide analysis of long noncoding RNA stability. Genome Res. 2012;22(5):885-898.

12. Fei Q, Bai X, Lin J, et al. Identification of aberrantly expressed long non-coding RNAs in postmenopausal osteoporosis. Int J Mol Med. 2018;41(6):3537-3550.

13. Hao L, Fu J, Tian Y, et al. Systematic analysis of IncRNAs, miRNAs, and mRNAs for the identification of biomarkers for osteoporosis in the mandible of ovariecetomized mice. Int J Mol Med. 2017;40(3):689-702.

14. Liu Y, Ferguson JF, Xue C, et al. Tissue-specific RNA-Seq in human evoked inflammation identifies blood and adipose LincRNA signatures of cardiometabolic diseases. Arterioscler Thromb Vasc Biol. 2014;34(4):902-912.

15. Sun L, Goff LA,Trapnell C, et al. Long noncoding RNAs regulate adipogenesis. Proc Natl Acad Sci USA. 2013;110(9):3387-3392.

16. De Tata V. Age-related impairment of pancreatic Beta-cell function: pathophysiological and cellular mechanisms. Front Endocrinol (Lausanne). 2014;5:138.
containing the Kunitz protease inhibitor. *Neurochem Int.* 2005;46(3):253-260.

270. Choi J, Levey AI, Weintraub ST, et al. Oxidative modifications and down-regulation of ubiquitin carboxyl-terminal hydrolase L1 associated with idiopathic Parkinson's and Alzheimer's diseases. *J Biol Chem.* 2004;279(13):13256-13264.

271. Holtzman DM, Herz J, Bu G. Apolipoprotein E and apolipoprotein E receptors: normal biology and roles in Alzheimer disease. *Cold Spring Harb Perspect Med.* 2012;2(3):a006312.

272. Pan JX. LncRNA H19 promotes atherosclerosis by regulating MAPK and NF-kB signaling pathway. *Eur Rev Med Pharmacol Sci.* 2017;21(2):322-328.

273. Lv J, Wang L, Zhang J, et al. Long noncoding RNA H19-derived miR-675 aggravates restenosis by targeting PTEN. *Biochem Biophys Res Commun.* 2018;497(4):1154-1161.

274. Voellenkle C, Garcia-Manteiga JM, Pedrotti S, et al. Implication of Long noncoding RNAs in the endothelial cell response to hypoxia revealed by RNA-sequencing. *Sci Rep.* 2016;6:24141.

275. Hu YW, Zhao JY, Li SF, et al. RP5-833A20.1/miR-382-5p/NFIA-dependent signal transduction pathway contributes to the regulation of cholesterol homeostasis and inflammatory reaction. *Arterioscler Thromb Vasc Biol.* 2015;35(1):87-101.

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