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Review

Roles of long noncoding RNAs in aging and aging complications☆

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ABSTRACT

Aging is a universal and time dependent complex biological process, characterized by a progressive physiological dysfunction and an increased vulnerability to death. Though the physiological process of aging is still not fully understood, several cellular and molecular mechanisms have been identified. Long noncoding RNAs is a class of regulatory ncRNAs with transcript lengths > 200 nucleotides. Discovery of this vast pool of regulators in mammalian genome supplies a new dimension to study and explore the aging process. In this review, we discuss the contribution of lncRNAs in aging and aging complications, and raise interest of serving lncRNAs as biomarkers and potential therapeutic targets to prolong health and ameliorate age-associated diseases. We hope understanding the roles of these high specificity and low conservation regulators in generating age-associated phenotypes might benefit human lifespan.

1. Introduction

Nowadays, population with longevity and life expectancy improvements is rapidly growing [1]. An international population reports issued by United States Census Bureau mentioned that 8.5% of the world population were aged older than 65-year old in 2015. Notably, the growth trends of world's old population will continue to expand, almost 60% more elders will expand in the following 15 years. By 2050, some countries will even experience a quadrupling of old population. Accordingly, aging and aging complications have arguably become the most common maladies of elderly population.

Characterized by a time-dependent declination of physiological function and an increased vulnerability to death, aging involves a very complicated physiological process, which as of today is still not fully understood. Start shortly after zygote formation and continues over different stages of lifespan, the aging process contributes to the decline of homeostatic capacity from the aspects of structural and functional aberrancies in genome, epigenetic or protein stability [2,3]. Genome determines life expectancy, and the genetic manipulations in various species can affect lifespan. For example, PI3K-null mutants in nematode could lead to nearly ten-fold extension of lifespan and much more resistant to stresses [4]. However, not all aging events could be explained by the genomic changes. Epigenetic regulations of DNA methylation, histone modifications and chromatin remodeling and nondcoding RNAs (ncRNAs) may be other candidates for aging process [5]. Viewed as new regulators for gene expressions, the large amounts of ncRNAs could be separated into short ncRNAs (mainly microRNAs, tRNAs) and long ncRNAs (lncRNAs) based on their transcript length. Recently, lncRNAs are paid more attention due to their high specificity and low conservation.

Advanced age is a main risk factor of most chronic diseases and degenerative pathologies, such as cancer, cardiovascular disease (CVD) and Alzheimer's disease (AD) [6]. The observation that elderly population usually demonstrates two or more aging complications with similar disease characteristics raises the possibility of age-related diseases (ARD) prevention, whenever clear the underlying mechanisms.

In this review we will comment on some lncRNAs that affect the process of aging and discuss their possible effects. We will also review lncRNAs that play roles in aging complications in order to make clear that these ncRNAs can be used as biomarkers and therapeutic targets.

2. Genetic aspect of aging

Dozens of genes with mutations or altered activities have been identified in aging process and, potentially, longevity. For example, LMNA gene encodes lanmin A could be applied to screen age-related clues, since mutation of this gene lead to decreased longevity [7]. Metabolic pathways of insulin/IGF-1, PI3K, TOR, MAPK are vital and

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associated with regulating the aging process [8]. Mutations in genes encode substrates, receptors, kinases of these pathways result into extended or shortened lifespan in animal models [9,10].

3. Epigenetic aspect of aging

Epigenetic mechanisms of DNA methylation, histone modifications, chromatin remodeling and nondcoding RNAs (ncRNAs) are all involved into aging [5].

DNA methylation, a process methyl groups are added to DNA molecules, is essential for normal development. Loss of genomic DNA methylation has been found in aging and a variety of aging complications. In mammals, at least three DNA methyltransferases (DNMTs) of DNMT1, DNMT3A and DNMT3B participate into the directly transfer of methyl group. Activities of DNMT1 and DNMT3A decreased whereas DNMT3B amounts notably increased with advanced age [11]. Besides, a reduction of 5-methyl-cytosine (5mC) content is observed in aged organisms, either in animal models or aged individuals [12,13].

Histones can be modified at different residues by respective modifications simultaneously. The post-translational histone modifications include methylation, acetylation, phosphorylation, ubiquitylation etc. Among these, acetylation catalyzed by histone acetyltransferases (HATs) generally associated with active gene transcription, and methylation catalyzed by histone methyltransferases (HMTs) linked to gene activation or repression are the two most widely studied markers [14]. For example, increased H3K9me3 level is with aging. Moreover, chromatin remodeling is reported to be closely linked to histone modifications.

With the advances in genome sequencing and microarray technology, numbers of genomes transcribed into RNAs without protein-coding potential are larger than expected. These RNAs named as ncRNAs, are initially regarded as junk RNAs, proving to play important roles in gene regulation [15].

3.1. LncRNAs

Long ncRNAs are a class of regulatory ncRNAs whose transcript lengths > 200 nucleotides [16]. They are generally transcribed in genome and acted as signals, decoys, guides or scaffolds to impact gene expression at diverse modes of chromatin remodeling, transcriptional regulation and post-transcriptional modification. Similar proceed manners are observed between lncRNAs and mRNAs, with RNA polymerase II occupancy, 5′-capped and 3′-polyadenylated structure and histone modifications associated with Pol II transcriptional elongation [17]. However, lncRNAs demonstrate much more specificity pattern. Little sequence or motif conservation among species or tissues is observed, either in strictly regulated physiological development and signaling response or pathological conditions. The specificity implies lncRNAs towards function diversity.

lncRNAs can be categorized into different groups due to its diversity. Based on genomic localization and transcription direction, lncRNAs could be classified into six categories (Fig. 1). Sense lncRNAs: expressed from the same direction of the adjacent protein coding genes; antisense lncRNAs: expressed from the opposite direction of the adjacent protein-coding genes; intronic lncRNAs: transcribed from the intron of a protein-coding gene; intergenic lncRNAs: transcribed from the gene fragment between two protein-coding transcripts; enhancer lncRNAs (eRNA): transcribed from the enhancer region of a protein-coding gene; circular lncRNAs: usually generated by a splicing machinery [18]. Based on their subcellular localization, lncRNAs could be divided into nuclear or cytoplasmic lncRNAs (Fig. 2). Nuclear lncRNAs is extensively implicated in chromatin remodeling, histone modifications, transcription as well as early post-transcriptional regulation such as alternative splicing [19–21]. Cytoplasmic lncRNAs are associated with diverse post-transcriptional regulation. They can interact with RNA binding proteins or RNAs to influence mRNA turnover, RNA localization, protein translation and stability [22]. The widely diverse mechanisms of lncRNAs indicate that lncRNAs biological functions in diseases need to be explored on a case-by-case basis.

3.2. Aging characteristics and their lncRNAs

Aging contains complicated physiological mechanisms of degenerative pathologies or hyperplastic pathologies; despite these two seeming opposite characteristics, a common phenomenon of cell senescence is partly linked with these mechanisms [23]. Cell senescence is an irreversible state of dormancy that no known physiological stimulations could promote cells reenter the cell cycle [24]. Senescent cells in normal tissues with advanced age are observed to lose replicative ability and halt cell cycles, which drive age-related pathology. Increased evidences demonstrate enhanced senescent cell numbers during aging [25]. Species of rodents, nonhuman primates and humans all get through this age-associated pathologies and physiological decline phenotype.

Cellular senescence could be triggered through two closely related processes: telomere erosion (replicative senescence) or exposure to damaging conditions (premature senescence) [26]. Replicative senescence (RS) arises from the loss of telomeres length, thereafter, delayed replicative senescence could be observed whenever restoring telomerase expression [27]. Premature senescence is shown to occur earlier than telomere depletion. This growth arrest could be induced by various hostile external conditions [28]. Despite the dichotomic mechanisms, senescent cells share identical patterns of enlarged cell morphology, growth arrest and elevated senescence-associated beta-galactosidase (SA-β-gal) activity [29]. In addition, some senescent cells also display a senescence associated secretory phenotype (SASP), with secreted factors of cytokines, chemokines and matrix metalloproteases [24]. In this part, we focus on aging characteristics and discuss roles of lncRNAs implicated in this pathogenesis (Table 1, Fig. 3).

3.2.1. Genomic instability and activation of DNA damage response (DDR) pathway and lncRNAs

Genome is a whole set of genetic material, with either genes or non-coding sequences important for gene regulation. Genome instability is a cause of aging. The instability refers to a general dysregulation of genomic changes accumulated in tissues and organs, which includes changes in nucleic acid sequences, aneuploidy and chromosomal rearrangements. Maintenance of genome integrity is essential for proper function and survival of all organisms.

A highly conserved *NORAD lncRNA* (*noncoding RNA activated by DNA damage*) with ubiquitous and abundant expression in human tissues is induced after DNA damage [30]. Inactivation of *NORAD* yields a chromosomal instability phenotype of aneuploidy in previously stable cell lines. Mechanically, *NORAD* acts as a multivalent binding platform to sequester the highly conserved RNA binding proteins of PUM proteins, which result in accelerated turnover and decreased translation of a set of transcripts through 3′UTR.

DNA damage is known to be involved into both of replicative senescence and premature senescence [31]. Inducers of exogenous stimulations of physical, chemical and biological agents as well as endogenous threats of reactive oxygen species (ROS), reactive nitrogen species are all potential DNA damage sources. To protect genome integrity after DNA damage, cells could start an efficient response to repair this lesion and maintain genomic integrity, a process named DNA damage response (DDR) [32]. The DDR signaling, with a causative role in the establishment of cellular senescence, contains a complex network and enzymes in the repair strategies of base excision repair, nucleotide excision repair, homologous recombinational repair (HR) and non-homologous end joining (NHEJ) [33].

A particular choice of DNA damage response after DNA double-strand breaks (DSBs) is important, since wrong options lead to a detrimental DNA repair outcome. *DDSR1* (*DNA damage-sensitive RNA1*)

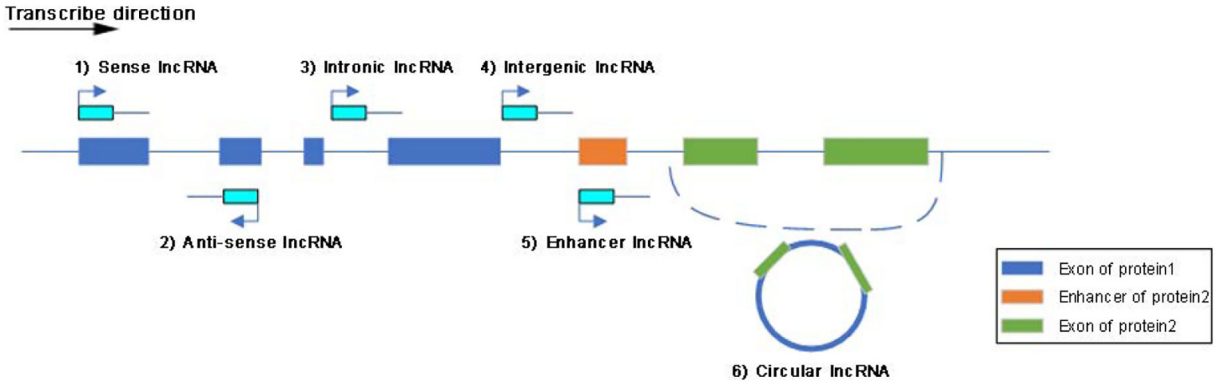

Fig. 1. Schematic diagram illustrating the lncRNAs classification based on genomic localization and transcription direction. (1) Sense lncRNAs: expressed from the same direction of the adjacent protein coding genes. (2) Antisense lncRNAs: expressed from the opposite direction of the adjacent protein-coding genes. (3) Intronic lncRNAs: transcribed from the intron of a protein-coding gene. (4) Intergenic lncRNAs: transcribed from the gene fragment between two protein-coding transcripts. (5) Enhancer lncRNAs (eRNA): transcribed from the enhancer region of a protein-coding gene. (6) Circular lncRNAs: generated by a splicing machinery.

lncRNA is a DNA damage regulator [34]. At early stage upon DSBs formation, enhanced *DDSR1* could sequester the increased accumulation of BRCA1/RAP80 complex around the DNA damage site and facilitate the repair pathway choice. Its function of DNA repair by promoting HR pathway and enhancing cell survival is acquired through interacting with BRCA1 and hnRNPUL1. Following the early stage, *DDSR1* is triggered through an ATM-NF-κB pathway-dependent manner by several DSBs agents and negatively regulates p53 target genes.

3.2.2. *p53/p21 and p16^{INK4a}/pRB pathways and lncRNAs*

Pathways of p53/p21 and p16^{INK4a}/pRB are involved into cellular senescence induction and senescence growth arrest maintenance, both of these two pathways are cross-regulated to each other [35,36].

For the p53/p21 pathway, p53 is a master transcriptional regulator, while p21 is its downstream effector [37]. During the process of DDR activation, typical activation response of p53/p21 could be observed [38]. In addition to senescent cells, changes of p53/p21 are also observed during the process of apoptosis or cell cycle arrest. Albeit not specific, p53/p21 as well as its downstream pathways could be used together with other senescence markers.

RoR (*lincRNA-RoR*), suppresses p53 translation through direct interaction with the hnRNP I (heterogeneous nuclear ribonucleoprotein I), is a strong negative regulator of p53 [39]. *RoR* is unique in the p53 pathway, and a *RoR*-p53 autoregulatory feedback loop is observed when p53 transcriptionally induces *RoR* expression.

The new component of the DNA damage response *DINO* (*Damage Induced Noncoding*) could stabilize p53 protein and mediates a p53 auto-amplification loop [40]. *DINO* was required for the p53-dependent response towards DNA damage, and its expression was sufficient to activate damage signaling and cell cycle arrest in the absence of DNA damage.

PANDA (*p21-associated ncRNA DNA damage activated*) *lncRNA*,

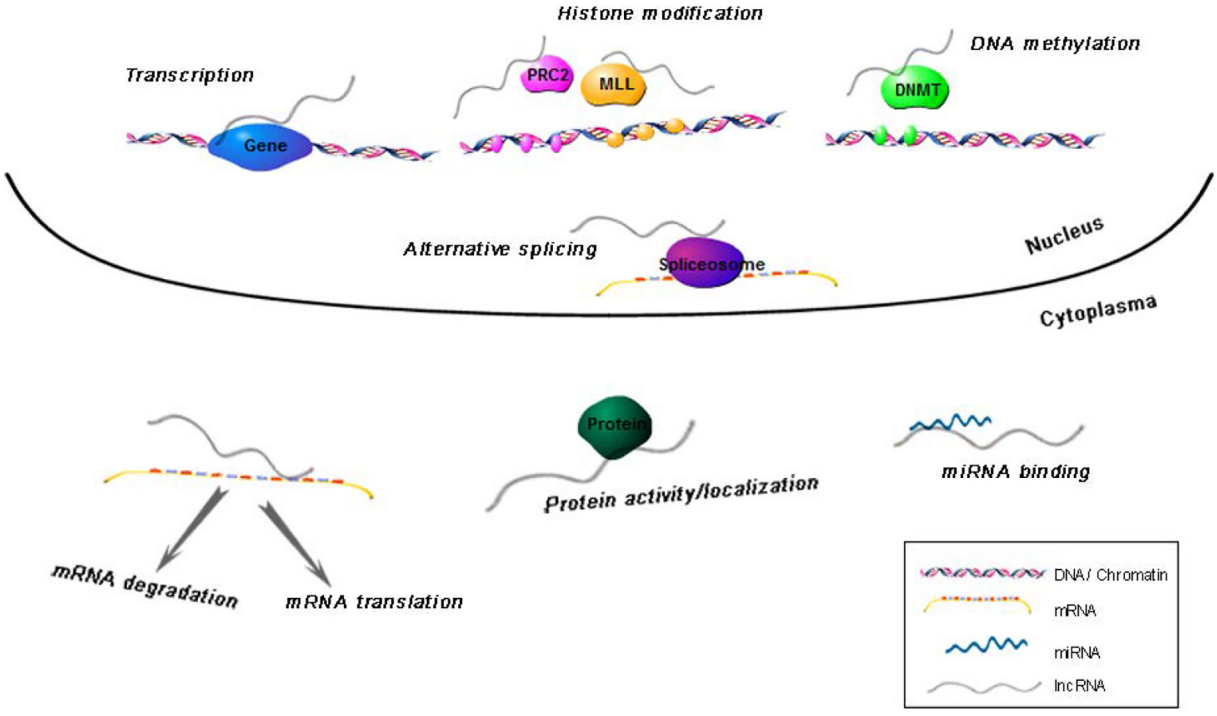

Fig. 2. Paradigms of nuclear and cytoplasmic lncRNAs functions. Nuclear lncRNAs is implicated in chromatin remodeling, histone modifications, transcription and regulation of early post-transcriptional steps; cytoplasmic lncRNAs can interact with RNA binding proteins, mRNAs, miRNAs or ribosomes to influence mRNA and protein.

Table 1
A list of lncRNAs involved in aging.

lncRNA	Species	Function	Targets	Mechanism	Reference
Genome instability and activation of DNA damage response (DDR) pathway					
NORAD	Human	Inactivation of *NORAD* yields aneuploidy,	PUM proteins	*NORAD* sequesters the highly conserved PUM proteins.	[30]
DDSR1	Human	Promote homologous recombinational repair pathway in DSBs	BRCA1 and hnRNPUL1	At early stage upon DSBs, enhanced expression of *DDSR1* sequesters the increased accumulation of BRCA1/RAP80 complex around the DNA damage site. Follow by the early stage, *DDSR1* is triggered through an ATM-NF-κB pathway-dependent manner by several DSBs agents and negatively regulates p53 target genes	[34]
p53/p21 and p16^{INK4a}/pRB pathways					
RoR	Human	A strong negative regulator of p53 in response to DNA damage	hnRNP I	Direct interacts with hnRNP I and suppress p53 translation	[39]
DINO	Mouse/ human	Induced in DNA damage	P53	Stabilize p53 protein and mediating a p53 auto-amplification loop.	[40]
PANDA	Human	Activated in DNA damage	NF-YA	Interact with the NF-YA to regulate apoptosis.	[41]
LincRNA-p21	Mouse	*lincRNA-p21* mediates gene silencing Upon DNA damage	hnRPK	Interact with the hnRPK to regulate p53-mediated gene repression.	[42]
MALAT1	Human	A p53 repressor	P53	p53 induction upon *MALAT1* depletion is a consequence of dsDNA damage response	[43]
ERIC	Human	Up-regulated in DNA damage	E2F1	E2F1 and *ERIC* constitutes a negative feedback loop of E2F1 activity modulation	[50]
ANRIL	Human	*ANRIL* modulates gene expression and DNA repair by homologous recombinational repair pathway	SUZ12	Represses INK4b expression via PRC2	[48,49]
Telomere shortening					
TERRA	Human	Regulates the structure and processing of deprotected telomeres	SUV39H1	Facilitates heterochromatin formation by accumulating H3K9 trimethylation at damaged telomeres, and induces an interaction of LSD/MRE11 to promote nucleolytic processing of uncapped telomeres	[53–55]
SAL-RNA1	Human	Delay senescence	N.A.	Reduced *SAL-RNA1* level can enhance senescence	[56]
Oxidative stress					
ASncmtRNA-2	Mouse	Induced in replicative senescence	NA.	Might participate in the cell cycle arrest in G2/M phase and through the production of hsa-miR-4485 and hsa-miR-1973	[57,58]
Senescence-associated secretory phenotype (SASP)					
SALNR	Human	Is reduced during cellular senescence	NF90	Interacts and blocks the NF90 nucleolus translocation, and finally rescues the inhibitory function of NF90 on senescence-associated miRNA biogenesis	[63]
Other lncRNAs related with aging					
HOTAIR	Human	Highly upregulated in cell senescence	Ataxin-1 Snurportin-1	Facilitates the ubiquitination of Ataxin-1 and Snurportin-1 in senescence cell and accelerates their degradation	[65]
GAS5	Human	Translation initiation	eIF4F complex	Translation regulation by binding with the eIF4F complex.	[67]
TTS-1	*C. elegans*	Reduce ribosome levels	NA.	Functions as a translation regulator of ribosomal protein mRNAs	[68]

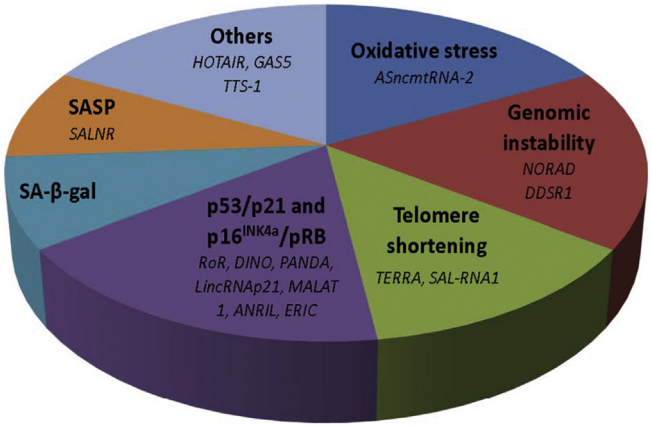

Fig. 3. Aging hallmarks and their lncRNAs. This scheme illustrates the aging characteristics and their lncRNAs described in this review.

transcribed from CDKN1A promoter, is transcribed together with p21 transcription in a p53-dependent manner and activated by DNA damage [41]. Chromatin immunoprecipitation analysis demonstrated that *PANDA* interacted with the transcription factor NF-YA to regulate apoptosis. *PANDA* knockout sensitized pro-apoptotic genes.

LincRNA-p21 transcribed from noncoding DNA sequences upon p53 binds at the CDKN1A locus [42]. Upon DNA damage, *lincRNA-p21* mediates gene silencing through recruitment of hnRPK. Knockdown of either p53 or *lincRNA-p21* would activate the cell viability, suggesting its direct physiological role in DDR.

MALAT1 (*Metastasis-associated lung adenocarcinoma transcript 1*), highly abundant in neurons, is identified to enhance cell proliferation and metastasis as a p53 repressor in a cell cycle-dependent manner [43]. Silenced *MALAT1* would activate the p53 pathway, and p53 is required for the *MALAT1* dependent cell cycle arrest. p53 induction upon *MALAT1* depletion could be a consequence of dsDNA damage response.

$p16^{INK4a}$, a cyclin-dependent kinase inhibitor and tumor suppressor that promotes growth arrest, is a widely used senescence marker [44]. This protein contributes to the acquisition of age-related pathologies in rodent models and humans, while its removal delayed the onset of these phenotypes [45]. $p16^{INK4a}$ could regulate cell cycle gene expression through preventing phosphorylation and inactivation of Rb protein, which forms a Rb-E2F complex [46]. During the process of UV or methyl methanesulfonate-induced DNA damage, Rb is dissociated from the complex through phosphorylation, and E2F1 stabilization is observed [47].

ANRIL (*Antisense non-coding RNA in the INK4 locus*) lncRNA, transcribed from the same locus of $p16^{INK4a}$-$p14^{ARF}$-$p15^{INK4b}$ but in an opposite direction, is induced by the E2F1 transcription factor in an ATM-dependent manner [48]. *ANRIL* modulates gene expression and DNA repair by homologous recombinational repair. At the late stage of the DDR, elevated *ANRIL* could return cells to normal state by inhibiting the expression of tumor suppressor $p16^{INK4a}$-$p14^{ARF}$-$p15^{INK4b}$, which forms a negative feedback loop between $p16^{INK4a}$-$p14^{ARF}$-$p15^{INK4b}$ and *ANRIL*. Moreover, *ANRIL* exerts transcriptional control through binding to the polycomb repressor complex 2 (PRC2) protein [49].

ERIC (*E2F1-Regulated Inhibitor of Cell death*) lncRNA is transcriptionally up-regulated by E2Fs and DNA damage [50]. Inhibition of *ERIC* expression facilitates E2F1-mediated apoptosis, suggesting a negative feedback loop of E2F1 and *ERIC* for modulating E2F1 activity.

3.2.3. Telomere shortening and lncRNAs

Telomeres are protective and dynamic chromosome-end complexes at the termini of chromosome, their length known to be one of the major determinants of aging and longevity in higher mammals [51]. Damages of chemicals, stress, nuclease actions or age-related deteriorations would contribute to telomere-shortening process, named telomere attrition. However, telomerase, a specialized RNA-dependent polymerase, has the capacity to compensate this process by replicating the terminal ends of linear DNA molecules. Telomerase reverse transcriptase (TERT), a catalytic subunit of the telomerase, together with the telomerase RNA component (TERC), comprises the most important unit of the telomerase complex. However, levels of telomerase in mammalian somatic cells are limiting, leading to the shortening of telomere all life [52].

The lncRNA *TERRA* (*telomeric repeat-containing RNA*) transcribed from telomeres has been shown to regulate the structure and processing of deprotected telomeres. *TERRA* transcript is driven by RNA polymerase II, linked with chromatin structure, partially colocalized with telomeres, and increased upon DNA damage [53]. Abnormal elevated expression of *TERRA* may relate with senescence and aging. A p53-dependent increase of *TERRA* level is reported at damaged telomeres [54], however, its upregulation at TRF2-null telomeres is independently of ATM-dependent checkpoints and p53 signaling. *TERRA* has been indicated to facilitate heterochromatin formation by accumulating H3K9me3 at the damaged telomeres, and the interaction of *TERRA* to SUV39H1 (a histone methyltransferase) is responsible for the methylation [53]. Moreover, lysine demethylase (LSD1) bound by *TERRA* would promote lysine demethylase-meiotic recombination 11 (LSD-MRE11) interaction, which then induce the nucleolytic processing of uncapped telomeres [55].

A novel senescence-associated lncRNA *SAL-RNA1* is found with lower abundance in replicative senescent cells and to delay senescence [56]. The reduced *SAL-RNA1* level enhanced the appearance of phenotypic traits of senescence of enlarged morphology, positive β-galactosidase activity and elevated p53 level.

3.2.4. Oxidative stress and lncRNAs

Mitochondria-derived ROS is an important player in senescence initiation. During the situation of enhanced senescent endothelia cells, induced expression of mtDNA-transcribed lncRNA, *ASncmtRNA-2*, is observed. *ASncmtRNA-2* forms a similar chimeric structure with *SncmtRNA* but contains an antisense fragment of *16S* rRNA transcribed from the L-strand [57]. Induction of its expression is driven by replicative senescence instead of stress-induced premature senescence, indicating this lncRNA might be telomere driven. In addition, *ASncmtRNA-2* might participate in the cell cycle arrest in G2/M phase and through the production of hsa-miR-4485 and hsa-miR-1973 [58].

3.2.5. Senescence-associated beta-galactosidase (SA-β-gal) and lncRNAs

Increased SA-β-gal activity is a common feature of senescent cells. The SA-beta-gal enzyme induction during senescence was due at least in part to increased expression of lysosomal beta-galactosidase (GLB1) gene [59]. SA-β-gal activity is now extensively used to identify senescence cells, however, in consideration of the disturbance of the staining duration and the cell density, the staining conditions should be strictly controlled. Up to now, no lncRNA is reported to be directly related with SA-β-gal activity.

3.2.6. Senescence-associated secretory phenotype (SASP) and lncRNAs

Senescent cells secrete a large complexity of cytokines, chemokines, growth factors and proteases into the extracellular environment through either autocrine signaling or paracrine signaling [60]. This senescence-associated secretory phenotype (SASP) promotes damaged cells to communicate with neighboring cells or to enhance immune system to clear damaged cells by inflammatory response, cell proliferation, new blood vessel formation and epithelial-to-mesenchymal transition [61,62]. Though SASP factors vary among cells and senescence-inducing stimulus, pro-inflammatory cytokines, such as IL-6 and IL-8, are the most highly conserved feature. The involvement of these inflammatory cytokines into other physiological and pathological

processes lead SASP not a specific marker, however, combined with other senescence characteristics, SASP could exert an important role, especially in the study of aging towards cell microenvironment.

SALNR (*Senescence-associated long non-coding RNA*) lncRNA is identified from a genome-wide screen of Ras-induced premature senescence [63]. Its regulation of senescence is achieved by the interaction and blocking of NF90 (nuclear factor of activated T-cells 90 kDa) nucleolus translocation, and finally rescues the inhibitory function of NF90 on senescence-associated miRNA biogenesis. NF90 is reported to repress the senescence-associated secretory phenotype [64].

Overall, so far, no single aging characteristic mentioned above is exclusive to the senescent cells, while not all senescent cells display all these senescence markers.

3.3. Other lncRNAs related with aging

In normal condition, the stability of lncRNA *HOTAIR* (*HOX antisense intergenic RNA*) is negative associated with HuR. However, during the process of cell senescence with declined HuR, *HOTAIR* is highly upregulated. *HOTAIR* forms complexes with two E3 ubiquitin ligases bearing RNA-binding domains, Dzip3 and Mex3b, as well as interacts with their respective ubiquitination substrates, Ataxin-1 and Snurportin-1 [65]. In this manner, *HOTAIR* facilitates the ubiquitination of Ataxin-1 and Snurportin-1 in senescence cell, accelerates their degradation, and preventing premature senescences.

Protein synthesis, especially translational initiation, is an essential way to replace damaged proteins with fresh ones. A translation initiation trimeric complex eIF4F, which is composed of eIF4G, eIF4E and eIF4A, is involved into the initiation step. *GAS5* (*Growth arrest-specific 5*) lncRNA is associated with translation initiation machinery and regulates translation by binding with the eIF4F complex (particularly the eIF4E) [66]. Its expression is remarkably enhanced in aged mice [67].

Inhibitions of either ribosomes biogenesis or the coordinated protein translation can extend lifespan. *TTS-1* (*transcribed telomeric sequence 1*) *lncRNA*, carry both of *daf-2* insulin receptor mutant and *clk-1* mitochondrial mutant, is found to reduce ribosome levels and promote life extension through different longevity pathways. Although the precise mechanism of *TTS-1* remains to be determined, it is speculated that this lncRNA functions as a translation regulator of ribosomal protein mRNAs [68].

4. LncRNAs in age-associated cardiovascular diseases

Advanced age is a main risk factor of most chronic diseases and degenerative pathologies, such as cancer, cardiovascular disease (CVD) and Alzheimer's disease (AD) [6]. Among these aging complications, cardiovascular disease (CVD) accounts for a relatively large proportion. CVD is characterized by detrimental changes of hypertrophy and diastolic dysfunction in heart, as well as declined dilation and enhanced oxi-inflammation in endothelium [69]. Hypertension, myocardial infarction, stroke, hypertrophy and heart failure are all belong to this aging complication. Various mechanisms are associated with this age-associated CVD system changes, including lncRNAs which can regulate gene expression and signaling pathways at different stages [70–72].

4.1. Myocardial infarction and lncRNAs

Myocardial infarction is far more common in the elderly. Five lncRNAs measured from human peripheral blood cells demonstrate that expressions of *aHIF*, *KCNQ1OT1, MALAT1* are higher and expression of *ANRIL* is lower in myocardial infarction (MI) patients than healthy volunteers. *ANRIL* and *KCNQ1OT1* could be prognostic markers for left ventricular function [73]. In MI mice model, two lncRNAs of *MIRT1* (*myocardial infarction-associated transcript 1*) and *MIRT2* are robustly up-regulated and correlate with genes involved in left ventricular remodeling and ejection fraction [74].

Acute myocardial infarction (AMI) is a serious cardiovascular disease with high morbidity and mortality. Its early diagnosis is crucial for therapeutic treatment and life saving. Circulating lncRNAs of *UCA1* (*urothelial carcinoma-associated 1*), *ZFAS1* (*Zinc finger antisense 1*), *CDR1AS* (*Cdr1 antisense*), *MHRT* (*Myosin Heavy Chain Associated RNA Transcripts*) *and HOTAIR* (*HOX antisense intergenic RNA*) are independent predictors and could be promising biomarkers for human AMI diagnosis and prognosis [75–78].

4.2. Heart failure and lncRNAs

The prevalence of heart failure (HF) increases with age. Mitochondrial *LIPCAR* (uc022bqs.1) lncRNA with chimeric fusion transcript of 5′-end of COX2 and 3′-end of CYTB is shown to be up-regulated in patients with chronic heart failure and later MI stages but down-regulated in early myocardial infarction stage [79]. lncRNAs of *ANRIL*, *HOTAIR* and *LOC285194*, significantly regulated in non end-stage and end-stage heart failure patients, showed similar modulation in peripheral blood mononuclear cells and heart tissue [80]. lncRNAs of *NRON* (*non-coding repressor of NFAT*) and *MHRT* (*myosin heavy-chain-associated RNA transcripts*) are significantly elevated in circulating plasma of HF patients [81]. These circulating lncRNAs could be prognostic indicators for heart failure and cardiovascular mortality.

In addition, microarray analysis of the cardiac lncRNA expression profile of the myocardial-specific pdk1-null heart failure mice model demonstrates that *MKK7*, a sense overlap lncRNA, is down-regulated in cardiomyocytes and involved in MAPK signaling pathway [82].

4.3. Hypertension and lncRNAs

A recent study by our group identified a human-specific, VSMCs-dominant *lncRNA-AK098656*. This lncRNA strongly upregulated in the plasma of hypertensive patients, directly binds with proteins of myosin heavy chain-11 and fibronectin-1 to facilitate their degradation. Resistance artery remodeling and elevated blood pressure are observed in *AK098656* transgenic rats. This first reported hypertensive causational lncRNA provide a potential therapeutic target for hypertension [83]. *GAS5* (*growth arrest–specific 5*), mainly expressed in ECs and VSMCs, is involved in blood pressure regulation and vascular remodeling. In the spontaneously hypertensive rats model, *GAS5* is significantly down-regulated, which intervenes β-catenin nuclear translocation [84].

4.4. Hypertrophy and lncRNAs

Sustained cardiac hypertrophy accompanied by maladaptive cardiac remodeling could lead to an increased risk of heart failure. *MHRT* (*myosin heavy-chain-associated RNA transcripts*) *lncRNA* is cardiac-specific and abundant in adult hearts. It can protect heart from hypertrophy and failure through a mechanism of *MHRT*-Brg1/BAF complex interaction [85].

LncRNAs of *CHRF* (*cardiac hypertrophy related factor*), *CHAER* (*cardiac-hypertrophy-associated epigenetic regulator*), *H19* and *CHAST* (*cardiac hypertrophy-associated transcript*) are all associated with cardiac hypertrophy in animal models. In angiotensin II treated hypertrophy mice model, *CHRF* acts as a direct endogenous sponge of miR-489 and downregulates its expression [86]; Besides, *CHRF* is reported to be a pathway target for Valsartan regulation to improve DOX-induced HF mice [87]. *CHAER* (*cardiac-hypertrophy-associated epigenetic regulator*) is shown to be necessary for the development of cardiac hypertrophy. Its inhibition before the onset of pressure overload substantially attenuates cardiac hypertrophy and dysfunction [88]. Levels of *H19* and *CHAST* are up-regulated in pathological cardiac hypertrophy [89,90].

Table 2
A list of human circulating lncRNAs in age-associated cardiovascular diseases.

lncRNA	Disease	Function	Reference
aHIF	MI	*aHIF* expression is higher in MI patients	[73].
KCNQ1OT1	MI	*KCNQ1OT1* expression is higher in MI patients, and could be prognostic markers for left ventricular function	[73].
MALAT1	MI	*MALAT1* expression is higher in MI patients	[73].
ANRIL	MI, HF	*ANRIL* expression is lower in MI patients and could be prognostic markers for left ventricular function. It is also significantly up-regulated in heart tissues and peripheral blood mononuclear cells of heart failure patients.	[73,80].
UCA1	AMI	*UCA1* decrease at the early state of AMI patients plasma and increased at day3 after AMI	[75]
ZFAS1	AMI	Circulating *ZFAS1* level is significantly lower in AMI	[76]
CDR1AS	AMI	Circulating *CDR1AS* level is markedly higher in AMI patients	[76]
MHRT	AMI	Cardiac-specific, *MHRT* is significantly elevated in the blood from AMI patients	[77]
HOTAIR	AMI, HF	*HOTAIR* expression is significantly decreased in the serum of AMI patients, and down-regulated in heart tissues and peripheral blood mononuclear cells of heart failure patients.	[78,80]
LIPCAR	MI, HF	*LIPCAR* is shown to down-regulate early after MI but up-regulated during later stages, and is elevated in patients with chronic heart failure	[79]
LOC285194	HF	*LOC285194* is significantly down-regulated in heart tissues and peripheral blood mononuclear cells of heart failure patients.	[80]
NRON	HF	*NRON* is significantly elevated in circulating plasma of HF patients	[81]
MHRT	HF, hypertrophy	*MHRT* is significantly elevated in circulating plasma of HF patients, and reduced in hypertrophic cardiomyopathy tissue.	[81] [85]
AK098656	Hypertension	A human-specific, VSMCs-dominant lncRNA, strongly upregulated in the plasma of hypertensive patients	[83]

5. LncRNAs as biomarkers and potential therapeutic targets for aging and aging complications

Compared with traditional biomarkers, the capabilities of high specificity in cells and tissues as well as easy detection in body fluids highlight the opportunities for lncRNAs to be convenient and minimally invasive diagnostic markers. A list of human circulating lncRNAs identified in age-associated CVD is summarized in Table 2.

Dietary and pharmacological interventions that benefit homoeostasis and rejuvenate diverse aspects of physiology have been confirmed to extend health and lifespan [91]. Among them, calorie restriction is the most robust strategy. Nutrients sensitive pathways of mechanistic target of rapamycin (mTOR) and insulin/insulin-like growth factor-1 signaling (IIS) pathway, together with energy sensitive pathways of AMP-activated protein kinase (AMPK) and the sirtuin enzymes have been implicated in calorie restriction [92]. However, given the characteristics of tightly transcriptional regulation, tissue-specific expression and disease dysregulation, lncRNAs targeting could be another treatment method of aging and aging complications with the advantages of more precise and minimize side effects.

RNA interference such as siRNAs is applied to down-regulate RNA expression previously; but recently, RNA silencing is becoming a more promising method. GapmeR, a newly developed tool for gene inhibition, is also able to efficiently down-regulate genes in the nucleus [90]. So, the dysregulated lncRNAs can be modified either by GapmeRs or antisense oligonucleotides. The modified 2′-MOE– and locked nucleic acid (LNA)-based antisense oligonucleotide (ASO) with enhanced RNA stability have been used to target lncRNAs in certain cellular compartments or tissues [93]. However, ASO binds towards lncRNAs is challenged due to the highly structured nature of lncRNAs. A second approach for lncRNA-based therapy is to disrupt the interactions of lncRNAs and their protein-binding partners by small molecule inhibitors [94]. Though targeting lncRNAs still faces challenges of low expression levels and low conservation across species, two FDA approved oligonucleotides of mipomersen and Fomivirsen treat homozygous familial hypercholesterolemia and cytomegalovirus retinitis, respectively, together with over 100 antisense oligonucleotide tested in clinical trials, put this lncRNAs-targeting therapy promising [94].

6. Conclusions and perspectives

Aging is characterized by progressive dysfunction of accumulations of molecular errors that increases disease susceptibility over time. The pathologies of aging can be modulated by lncRNAs via transcriptional, post-transcriptional or post-translational processes. In this review, we describe roles of lncRNAs in the aging and aging complications, trying to elucidate their comprehensive mechanisms in physiological and pathological functions.

LncRNAs have been a new hotspot in aging disease research. They are illustrated to be much more specific and complex than other ncRNAs or coding genes from the views of regulation. Although thousands of lncRNAs and transcription profiles have been identified through genome-wide analysis, only a minority of them is functionally clarified. Suitable lncRNAs with overlapped known genes, with high tissue specificity and with large differential expressions in disease state could be chosen as potential candidate to explore functions in the future. In addition, loci or genes regulated by lncRNAs through high throughput methods could also be deeply explored. However, great challenges still exist when we discuss the roles of lncRNAs in the diseases pathophysiology. For example, what's the relationship between lncRNA structure and its function, how to establish a causational relationship between lncRNA and aging-associated alternations, how to select suitable animal models if there are no homologous sequences among different species.

Transparency document

The Transparency document associated with this article can be found, in online version.

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