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Long noncoding RNAs in Diseases of Aging

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Abstract

Aging is a process during which progressive deteriorating of cells, tissues, and organs over time lead to loss of function, disease, and death. Towards the goal of extending human health span, there is escalating interest in understanding the mechanisms that govern aging-associated pathologies. Adequate regulation of expression of coding and noncoding genes is critical for maintaining organism homeostasis and preventing disease processes. Long noncoding RNAs (lncRNAs) are increasingly recognized as key regulators of gene expression at all levels – transcriptional, post-transcriptional and post-translational. In this review, we discuss our emerging understanding of lncRNAs implicated in aging illnesses. We focus on diseases arising from age-driven impairment in energy metabolism (obesity, diabetes), the declining capacity to respond homeostatically to proliferative and damaging stimuli (cancer, immune dysfunction), and neurodegeneration. We identify the lncRNAs involved in these ailments and discuss the rising interest in lncRNAs as diagnostic and therapeutic targets to ameliorate age-associated pathologies and prolong health.

Keywords

senescence; age-associated disease; ribonucleoprotein complexes; transcriptional control; post-transcriptional gene regulation; differentiation; myocytes; mRNA translation; mRNA stability; transcriptome

1. INTRODUCTION

Aging is a complex biological process during which the function of cells, tissues, and organs declines progressively, leading to a reduction in normal activity and an increase in age-related diseases [1, 2]. These declines can be categorized in a variety of ways, but they are generally believed to arise from changes in tissue composition leading to imbalanced energy metabolism, homeostatic dysregulation, and neurodegeneration [3]. Aging phenotypes are driven by changes in gene expression programs. Although such programs are robustly

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regulated by classic regulators of gene expression, such as DNA- and RNA-binding proteins, there is rising recognition that a new class of potent gene regulatory factors, noncoding RNAs (lncRNAs), also directly and profoundly affects gene expression programs with aging.

1.1. LncRNAs

ncRNAs of all sizes have been known for several decades [4-8]. However, the advent of high-throughput methodologies has provided a comprehensive view of the vast collection of ncRNAs which are pervasively transcribed across more than 75% of genome [9, 10]. This large and heterogeneous class of transcripts contains many small RNAs, including small nucleolar RNAs (snoRNAs), microRNAs (miRNAs), small interfering RNAs (siRNAs), small nuclear RNAs (snRNAs), and Piwi-interacting RNA (piRNA), but the vast majority of ncRNAs are longer than 200 nt and are thus designated as long ncRNAs (lncRNAs) [11-13]. LncRNAs have emerged as potent regulators of gene expression at different levels, including chromatin remodeling, transcriptional control, mRNA stability, mRNA translation, microRNA function, and protein metabolism [12, 14-16]. Through their influence on gene expression, lncRNAs are increasingly recognized as players with essential roles in molecular and cellular processes such as proliferation, apoptosis, differentiation, and senescence; in this regard, the impact of lncRNAs on the cellular and molecular basis of aging was recently reviewed [17]. LncRNAs also underlie important pathologic processes that increase with aging, including metabolic imbalances, neurodegeneration, cardiovascular disease, and cancer [18-23].

1.2. LncRNA classification and function

Unlike protein-coding RNAs and small regulatory RNAs, lncRNAs show little sequence or motif conservation among species [12, 24, 25]. Instead, the genetic position relative to protein-coding sequences and their functional conservation are considered to be important features to understand lncRNA biology and function [11, 12, 26, 27]. There is no universally adopted method to classify lncRNAs, but based on their transcriptional position and direction, lncRNAs can be categorized as antisense, intronic, intergenic, and divergent lncRNAs [28]. Antisense lncRNAs are synthesized in reverse direction relative to the protein-coding mRNA, resulting in overlaps of varying lengths between the two transcripts, and intronic lncRNA transcripts are transcribed from introns of a parental gene [28, 29]. Long intergenic lncRNAs (lincRNAs) are those with annotated positions localized between two protein-coding genes and are at least 5 kb away from protein-coding genes [11, 12, 28, 30, 31]. Finally, divergent lncRNAs are short transcripts usually synthesized from the promoter region of a protein-coding mRNA, but in the opposite direction [32].

Despite the fast progress in lncRNA transcript identification and annotation [33, 34], elucidating their molecular and biological roles has been challenging and, thus far, they have proven to vary widely [35]. Nonetheless, some functions are beginning to emerge. Nuclear lncRNAs have been extensively implicated in chromatin remodeling, histone modification, X-chromosome inactivation, transcription, splicing, imprinting, and nuclear organization [36-39]. These nuclear functions are achieved by the lncRNA-mediated recruitment of chromatin modifiers to specific chromatin regions, sometimes guided by the lncRNA to a

specific DNA site, with the lncRNA serving as a scaffold for the assembly of multiple chromatin modifiers [36-39]. LncRNAs can also be directly implicated in the process of pre-mRNA transcription, as shown for lncRNAs transcribed from enhancer regions (enhancer lncRNA [eRNA]), promoter regions (promoter-associated lncRNA [paRNA]), and transcriptional start site regions (transcription start site-associated lncRNA [TSSaRNA]) [40]. LncRNAs can also bind to nascent pre-mRNAs and influence their splicing and processing [41]. Cytoplasmic functions of lncRNAs include many diverse post-transcriptional steps [15]. LncRNAs can interact with RNA-binding proteins (RBPs), microRNAs and mRNAs to function as decoys or sponges, influence mRNA turnover rate, subcytoplasmic mRNA localization, and translation of target mRNAs [15, 42, 43], affect the stability of certain proteins by assembling components of ubiquitin-mediated proteolysis [16, 44, 45], and affect protein function by serving as scaffolds to assemble multiprotein complexes [41]. These examples illustrate the rich and versatile mechanisms whereby lncRNAs affect gene expression virtually at all levels –from early changes in chromatin architecture to the proteolysis of encoded proteins. In this review we focus on lncRNAs implicated in age-related diseases, their mechanism of actions and possible future interventions.

2. DISEASES OF AGING ASSOCIATED WITH DECLINING ENERGY METABOLISM

With advancing age, there is an overall decline in the body's ability to store energy, mobilize energy stores, sense changes in energy availability, and utilize energy. The age-associated increases in adiposity, reduced pancreatic function, and loss of muscle mass lead to major pathologic conditions seen in the elderly. In this section, we discuss lncRNAs implicated in the pathogenesis of diabetes and obesity [46, 47] as well as conditions arising from mitochondria dysfunction and muscle loss (Table 1).

2.1. LncRNAs affecting fat metabolism

The distribution and function of the adipose tissue change dramatically throughout life. Besides its immune and endocrine actions and its roles in thermoregulation, mechanical protection, and tissue regeneration, the adipose tissue is a major source of energy. The size of the adipose tissue increases during the adult years and has mainly a subcutaneous distribution. It declines in old age and progressively adopts a visceral distribution with accumulation in the liver, muscle, and bone marrow [48-51]. This extensive remodeling is accomplished by developmental processes governed by transcriptional regulatory factors whose expression and function are impaired with aging: the CCAAT/enhancer binding protein (C/EBP) β , peroxisome proliferator-activated receptor (PPAR) γ , and C/EBP α [52]. Posttranscriptionally, adipogenesis is also regulated by RBPs such as Sam68 [53] and by numerous miRNAs, reviewed in [54]. In this section we discuss lncRNAs involved in controlling fat tissue metabolism and adipogenesis.

Sun and colleagues [55] first identified lnc-RAPs as lncRNAs that showed regulated expression during adipogenesis. Among ~175 lnc-RAPs upregulated during differentiation, the pro-adipogenic transcription factors PPAR γ and CEBP α were found to bind to the promoter regions of 23 and 34 of them, respectively. Silencing lnc-RAPs 1 through 9

impaired adipogenesis, as determined by a lower accumulation of lipid and reduced expression of adipogenic markers including PPAR γ [55]. The direct impact of individual lnc-RAPs on aging of adipose tissue warrant direct study, particularly as PPAR γ levels decline in advancing age [56].

LncRNA *Firre* (functional intergenic repeating RNA element), also known as *lnc-RAP-1* was shown to interact in *trans* with chromosomes 2, 9, 15, and 17 in regions overlapping with genes *Slc25a12*, *Eef1a1*, *Atf4*, and *Ppp1r10*, all encoding adipogenic proteins. *Firre* also interacts with hnRNP (heterogeneous nuclear ribonucleoprotein) U in mouse adipose tissue and in adipocyte lysates. Downregulation of hnRNP U disrupted *Firre* localization on the inter-chromosomal loci, suggesting that *Firre* helps organize the nuclear architecture across chromosomes [57]. The potential impact of *Firre* on age-related adipose tissue function remains to be investigated.

naPINK1 is a natural antisense lncRNA to *PINK1*, a gene that encodes a PTEN (phosphatase and tensin homologue deleted on chromosome 10)-induced putative kinase 1. A mitochondrial kinase, PINK1 protects cells against oxidative stress-induced apoptosis and displayed aberrant function in age-related diseases like diabetes and neurodegeneration [58, 59]. Gene expression analysis of skeletal muscles indicated that *PINK1* mRNA was expressed with a pattern opposite to that of *naPINK1*. In healthy volunteers, inactive muscle expressed low *PINK1* mRNA and high *naPINK1*, while endurance training elevated *PINK1* mRNA and lowered *naPINK1* expression levels [60]. Since the *PINK1* locus, linked to neurodegenerative disease, is dysregulated during inactivity, obesity, and type 2 diabetes [60], disruption of *naPINK1* expression may impact upon these common age-related disease processes.

The lncRNA *H19* controls imprinting of a conserved cluster of genes that includes *IGF2* (insulin-like growth factor 2), involved in fat metabolism and fat deposition. In adult mice, low *Igf2* abundance was associated with increased fat deposition and occasional obesity, while loss of imprinting of the *Igf2-H19* locus during aging was found to enhance the expression of IGF2 and *H19* [61]. This regulatory paradigm in old prostate tissue was linked to cancer [62], but the age-related alteration may be associated broadly with fat deposition and metabolism.

Other lncRNAs related to adipogenesis have also been identified. For instance, *linc-DMRT2* and *linc-TP53I13* are regulated by lipopolysaccharide and downregulated in adipose tissue of obese humans [63]. Future studies will establish the function of lncRNAs in age-related diseases derived from loss of homeostasis of the adipose tissue.

2.2. LncRNAs affecting diabetes

Type 2 diabetes (T2D) increases in the elderly, accelerating the body's impairment in sensing energy levels, storing energy, and mobilizing energy out of storage [64-66]. A correlation between T2D and aging of pancreatic islet cells has been proposed to account at least in part for the rise in T2D in the elderly [67-69]. T2D is characterized by insulin resistance and low levels of circulating insulin, which reduces the availability of energy from glucose in peripheral tissues and elevates circulating glucose levels, causing other

important problems like stroke, atherosclerosis, and heart attack [70]. Numerous lncRNAs were identified in human β cells, and many of them have been dynamically integrated into diabetes-regulatory programs [71]. Transcriptome-wide sequencing of pancreatic β -cells and islets of Langerhans identified several lncRNAs that might be involved in the development or progression of age-related diabetes [72, 73]. However, their exact function in diabetes remains to be investigated. In this section, we explore lncRNAs that may have an impact on diabetes.

Compared with the levels in control individuals, diabetic individuals displayed higher levels of lncRNA *KCNQ1OT1* and lower levels of lncRNA *HI-LNC45* in pancreatic islets. In addition, the levels of lncRNAs *HI-LNC78* and *HI-LNC80* in islet cells increased in the presence of high glucose, indicating that these lncRNAs may be involved in sensing blood glucose levels [74]. The lncRNA *HI-LNC25*, also selectively expressed in islets and β cells, enhanced the levels of *GLIS3* mRNA, which encodes the GLIS3 transcription factor [74]. GLIS3 is required for normal β -cell function in adults [75]. Future studies are needed to fully understand the roles of these lncRNAs in diabetes.

Also known as *CDKN2B-AS1*, the lncRNA *ANRIL* interacts with PRC (polycomb repressive complex)1 and PRC2 to suppress transcription of the tumor suppressors and senescence inducers p16^{INK4A} and p15^{INK4B} [76-79]. Accordingly, silencing *ANRIL* in fibroblasts inhibited proliferation and triggered senescence [78]. Genome-wide association studies (GWAS) identified *ANRIL* as a hotspot of mutations in T2D [76, 80], suggesting that *ANRIL* may also contribute to regulating β cell proliferation capacity with age.

2.3. lncRNAs affecting diseases of mitochondrial dysfunction

The gradual age-driven decline in mitochondrial function causes tissue damage, reduces lifespan, and triggers a number of diseases such as myopathies, neuropathies, and diabetes [81, 82]. Several mitochondrial lncRNAs have been identified, such as *LNCND5*, *LNCND6*, and *LNCCYTB*, and they appear to be involved in mitochondrial gene regulation [83-85]. Additionally, some nuclear-encoded lncRNAs, such as *RMRP*, can be transported from the nucleus to the mitochondria and regulate mitochondrial gene expression and other mitochondrial functions [86]. Thus, mitochondrial lncRNAs involved in maintaining healthy and functional mitochondria may provide important information for aging-associated declines and pathologies.

Myocardial infarction and congestive heart failure are far more common in the elderly [87]. In a recent study, global transcriptome analysis of plasma RNA indicated that the mitochondrial lncRNA *LIPCAR* is downregulated early after myocardial infarction (MI), is upregulated during later stages following MI, and its levels in circulation may predict survival in patients with heart failure [88, 89]. Future analysis will ascertain the relevance and function of *LIPCAR* in age-related cardiovascular pathologies, as well as the decline in mitochondrial function with age [90] in this system.

2.4. LncRNAs affecting age-associated muscle pathology

Muscle dysfunction is commonly observed in the elderly, leading to the aging-associated frailty and sarcopenia [89]. Numerous lncRNAs associated with age-related muscle disorders are emerging.

The aforementioned imprinted lncRNA *H19* is implicated in cellular differentiation [92]. *H19* is expressed from the maternal allele and is highly abundant in embryonic tissues. Unlike most tissues, which experience strong repression of *H19* levels after birth and throughout old age, skeletal muscle maintains high *H19* levels, suggesting an important role of *H19* in skeletal muscle function [92]. *H19* and its encoded miRNAs, miR-675-3p and miR-675-5p, are upregulated during myoblast differentiation *in vitro* and muscle regeneration *in vivo*. *H19* promotes muscle differentiation in mouse and human primary muscle cells and in cultured C2C12 mouse myoblasts. In addition, miR-675-3p and miR-675-5p mediate *H19* function in muscle differentiation and regeneration by negatively regulating the bone morphogenetic protein (BMP) pathway, the transcription factors SMAD1 and SMAD5, and the DNA replication initiation factor CDC6 [92]. Similarly, *H19* can bind let-7 and limit its availability, acting as a molecular sponge; the decreased levels of *H19* levels in muscle from T2D individuals and in response to acute hyperinsulinemia increases let-7 availability in muscle cells [93, 94]. Thus, *H19* may have an essential role in skeletal muscle regeneration, a process that is impaired in the elderly.

The muscle-specific *linc-MD1* displays a decoy activity for miR-133, limiting its repressive impact on the *Elavl1* mRNA (encoding the RBP HuR) in mouse myoblasts [95]. A feed-forward regulatory mechanism was suggested, whereby HuR enhanced *linc-MD1* sponge activity by facilitating its recruitment of miR-133 and miR-135 and thereby modulated differentiation [96]. HuR is expressed at low levels in differentiated muscle and plays a direct role in muscle wasting and sarcopenia [97-99]. Thus, *linc-MD1* functions during the decline in muscle regeneration via HuR.

SIRT1 AS is a natural antisense lncRNA that was recently found to play a role in myogenesis. The levels of *Sirt1* mRNA and *Sirt1 AS* lncRNA decrease gradually during C2C12 myogenic differentiation. Overexpression of *Sirt1 AS* enhanced the levels of the NAD-dependent deacetylase SIRT1 (sirtuin-1). Interestingly, downregulation of SIRT1 by miR-34a was opposed by *Sirt1 AS* in C2C12 cells [100]. The fact that SIRT1 helps prevent senescence and aging [101], specifically maintaining a robust myogenic program [102], connects *Sirt1 AS* with muscle aging.

The levels of *MALAT1* (metastasis-associated lung adenocarcinoma transcript 1) rise during differentiation of mouse and human muscle cells, and *MALAT1* silencing suppressed the proliferation of myoblasts and endothelial cells [103, 104]. *Malat1* levels declined significantly following treatment of mouse gastrocnemius muscle with recombinant myostatin [103]. Given the impact of myostatin deficiency on muscle performance with age [105, 106], these findings suggest that *MALAT1* may be a downstream target of myostatin and a regulator of myogenesis influencing muscle aging.

The transcription factor YY1 (YIN YANG 1) was implicated in diseases that involve muscle weakness and wasting, including cancer, diabetes and chronic heart failure [107]. Genome-wide mapping of the binding sites of transcription factor YY1 in C2C12 myoblasts revealed a large YY1-regulated lincRNA locus that included the muscle-associated lincRNA *Yam-1*. YY1 repressed myogenesis at least in part by promoting the expression of *Yam-1*, which harbored the microRNA miR-715. Increasing *Yam-1* elevated miR-715 abundance in myoblasts, which in turn repressed production of a key target, the myogenic factor WNT7b [108]. By contrast, the lincRNA *Dum* [developmental pluripotency-associated 2 (DPPA2), upstream binding muscle lincRNA] activates myogenesis in C2C12 myoblasts [109]. Following transcriptional activation by the myogenic transcription factor MYOD, *Dum* interacts with DNA methyltransferases leading to the silencing of the neighboring gene DPPA2, which encodes a repressor of myogenesis [109].

3. DISEASES OF AGING ARISING FROM LOSS OF HOMEOSTASIS

The ability of the body to restore functions and internal homeostasis declines with age, leading to the development of cancer and other diseases associated with impaired ability to respond to cell and tissue damage [110-112]. In this section, we review examples of lncRNAs associated with cancer and the stress and immune responses (Table 2).

3.1. LncRNAs affecting cancer

LncRNAs have been implicated in carcinogenesis, which rises with advancing age. More than 70% of cancer cases are expected to be diagnosed in people aged over 65 years old by 2030 [113]. Here, we review the involvement of lncRNAs in cancer.

As mentioned earlier, *H19* plays roles in proliferation, cancer cell growth, apoptosis, and aging, and is regulated via imprinting of the *Igf2/H19* locus [114-118]. Loss of imprinting during aging of prostate tissues enhanced the expression of *H19* and IGF2, a factor linked to aging and cancer [62, 119]. Expression of *H19* is elevated in several human malignancies, including bladder, breast and colon cancers. *H19* is highly expressed in low-grade bladder carcinoma patients, suggesting that *H19* can be used as a marker for early recurrence in bladder carcinoma and metastasis [120, 121]. Expression of *H19* and the inhibitor of DNA binding/differentiation 2 (ID2) correlated positively in bladder cancer, and *H19* overexpression increased bladder cancer growth at least in part by elevating ID2 expression levels [122]. In breast cancer, the oncoprotein MYC, which is involved in cancer cell senescence, binds to and facilitates histone acetylation and transcriptional initiation of the *H19* promoter [123, 124]. Overexpression of *H19* enhanced breast cancer cell tumorigenesis and subcutaneous injection of *H19*-overexpressing breast cancer cells into immunodeficient (scid) mice showed that *H19* overexpression promotes tumor formation and progression [125]. Both *H19* and the microRNA it harbors, miR-675, are upregulated in human colon cancer cell lines and primary human colorectal cancer. miR-675 lowers expression of the tumor suppressor pRB (retinoblastoma protein) and inhibiting miR-675 reduced colon cancer cell growth and colony formation [126]. These findings suggest that *H19* enhances tumorigenesis at least in part via miR-675.

The lncRNA *MEG3* lowers cell proliferation by reducing the abundance of MDM2, an inhibitor of the tumor suppressor TP53 [127]. *MEG3* is highly expressed in normal liver, but is weakly expressed in liver cancer and pituitary cancer [128-130]. Ectopic expression of *MEG3* suppressed the growth of cancer cell lines HeLa, MCF-7, and H4, and hepatocellular carcinoma (HCC) [131, 132] and downregulation of *MEG3* in bladder cancer increased cell proliferation and inhibited apoptosis [130], supporting a tumor suppressor function for *MEG3*.

Human *MALAT1* is downregulated in senescent cells, and its silencing in young cells triggered cell senescence by enhancing TP53 expression [133, 134]. The oncogenic influence of *MALAT1* was associated with its ability to modulate serine/arginine (SR) splicing factors, which are closely associated with senescence and aging [135, 136]. The notion that altered *MALAT1* levels may impact upon tumorigenesis is supported by its high expression levels in several cancers, including lung and liver carcinoma [137, 138].

ANRIL promotes cell cycle arrest and inhibits senescence by repressing transcription of the tumor suppressor gene *p15 (INK4B)* [77, 78, 139]. GWAS analysis identified *ANRIL* as a risk locus for several cancers including breast carcinoma [76, 80]. Indeed, *ANRIL* was upregulated in prostate cancer cells, promoted non-small cell lung cancer cell proliferation by lowering expression of KLF2 and p21, and was proposed to be a marker of poor prognosis in gastric cancer [140-142]. Interestingly, *ANRIL* promoted tumor growth by preventing the action of miR-99a, a microRNA that inhibits HCC cell proliferation, and miR-449a, which induces prostate cancer cell cycle arrest and senescence [143, 144].

The Hox antisense intergenic RNA (*HOTAIR*) [143] regulates gene expression via polycomb-dependent chromatin modification and ubiquitin-mediated proteolysis [16, 146], and has been implicated in cell proliferation, senescence, and cancer [147]. Its oncogenic function is largely mediated by the recruitment of chromatin modifiers such as PRC2 to alter histone H3 trimethylation at lysine 27 (H3K27me3) and modulate gene transcription. *HOTAIR* levels are associated with poor prognosis in colorectal, cervical and endometrial carcinomas [146, 148, 149]. It is highly expressed in primary breast tumors and metastases and appears to serve as a predictor of metastasis and death [150].

The lncRNA *XIST* (X inactive-specific transcript) regulates dosage compensation that balances X-linked gene expression between males and females [151]. *XIST* is downregulated in senescent cells and upregulated in breast cancer, where the numbers of *XIST*-covered domains in chromosomes correlates with genetic abnormalities [152]. *XIST* levels correlate with Taxol sensitivity, thus possibly serving as a marker for chemotherapeutic responses in ovarian cancer [153].

BCYRN1 (brain cytoplasmic RNA 1, *BC200*) is a 200-nt-long ncRNA originally identified as a neuronal RNA. *BCYRN1* levels decrease by >60% in cortical areas between the ages of 49 and 86, but is upregulated in AD brains compared to age-matched normal brains, as mentioned below (section 4) [154]. *BCYRN1* is highly expressed in cancers of the breast, cervix, esophagus, lung, ovary, parotid, and tongue, but not in the corresponding normal

tissues [155, 156]. These data suggest that altered expression of *BCYRN1* is associated with both age-associated cancer and neurodegeneration.

Another lncRNA associated with both cancer and neurodegeneration, the growth arrest-specific 5 (*GAS5*), suppressed cell growth by acting as decoy for the transcription factor glucocorticoid receptor (GR), and thereby inhibited gene expression and induced apoptosis [157]. *GAS5* was found to be downregulated in human HCC and breast cancer [158]. These data suggest that low *GAS5* expression levels may promote tumorigenesis.

MIR31HG (*LOC554202*) harbors miR-31, a microRNA upregulated in senescent HUVECs (human umbilical vein endothelial cells) [159, 160]. miR-31 is downregulated in various cancers, including ovarian carcinoma and chronic myeloid leukemia cells, wherein miR-31 modulated cell proliferation and survival [161-164]. These findings suggest that *MIR31HG* and miR-31 are expressed with similar patterns [159], and its upregulation in senescent cells might be required to suppress tumorigenesis. It is not clear if *MIR31HG* functions in cancer independently of miR-31.

The lncRNA *7SL* is highly expressed in several cancers [155]. Although its impact on aging has not been studied directly, *7SL* silencing promoted autophagy and senescence, both hallmarks of aging and growth suppression [17]. *7SL* competes with HuR for binding to *TP53* mRNA and thus suppresses TP53 translation [43], supporting the notion that *7SL* can promote tumorigenesis by reducing the levels of a major tumor suppressor protein.

Numerous additional lncRNAs associated with tumorigenesis have been reported (reviewed in [165]). For instance, *HULC* is highly expressed in hepatocytes, HCC, and colorectal carcinomas that metastasize in the liver and may function in liver cancer by sponging miR-372 [166, 167]. Hypoxia-induced histone deacetylation lowered the production of *lncRNA-LET* ('low expression in tumor') in several cancers including carcinomas of the liver, lung, and colon. Ectopic expression of *lncRNA-LET* inhibited metastases in a mouse xenograft model, while its depletion increased invasion [44]. Lowering *lncRNA-LET* was also associated with the stabilization of the nuclear factor 90 protein (NF90), which is required for hypoxia-induced cancer cell invasion and for the senescence-associated secretory phenotype (SASP) [168]. The lncRNA *PCGEM1* (prostate cancer gene expression marker 1) was upregulated in prostate cancer and inhibited doxorubicin-induced apoptosis in LNCaP cells by reducing the levels of TP53, p21, cleaved caspase 7, and cleaved PARP [169, 170], suggesting that *PCGEM1* may regulate cellular senescence. Like *H19*, the oncogenic lncRNA *PVT1* is upregulated by MYC and is highly expressed in transformed cells [171]. Inhibition of *PVT1* or MYC expression inhibited proliferation and induced apoptosis of breast and ovarian cancer cell lines. In addition, the enhancement in *PVT1* levels was associated with reduced survival in patients treated with apoptotic agents [172]. The direct involvement of these lncRNAs in age-associated processes is unknown.

3.2. lncRNAs and the declining stress response

Environmental stress can cause an accumulation of cellular damage and disruption of cell functions leading to an acceleration of organismal aging. Thus, adequate responses to stresses such as DNA damage and unfavorable oxygen concentration are crucial for

enhancing cell survival, preventing age-related disorders, and increasing lifespan [173, 174]. The levels of many lncRNAs change following exposure to stress agents, in turn affecting various cellular responses. In this section, we will review the regulatory function of lncRNAs in stress responses relevant to the aging process.

A number of TP53-inducible lncRNAs were characterized by the Rinn laboratory [175]. Among them, *lincRNA-p21* mediated TP53-dependent transcriptional repression, as depletion of *lincRNA-p21* inhibited apoptosis and cell cycle arrest after doxorubicin treatment, while *lincRNA-p21* overexpression promoted spontaneous apoptosis in the absence of stress. *LincRNA-p21* elicited these effects by interacting with the RBP hnRNP K to repress TP53-target gene transcription [176]. Depletion of *lincRNA-p21* inhibited the production of lactate and glucose by hypoxia and reduced the levels of mRNAs encoding LDHA (lactate dehydrogenase A) and GLUT1 (glucose transporter 1). *LincRNA-p21* expression levels were induced by hypoxia and HIF-1 α (hypoxia-inducible factor 1 α) in many human cancer cell lines; reciprocally, silencing *lincRNA-p21* destabilized HIF-1 α protein levels by increasing its ubiquitination and degradation [45]. In addition, *lincRNA-p21* interacts with and suppresses the translation of *CTNNB* and *JUNB* mRNAs [177] (encoding the proliferative, senescence-inhibitory factor β -catenin [178] and the broad modulator proliferation JUNB [179], respectively) by recruiting the translation repressors RCK and FMRP [177]. Further roles of stress-inducible *lincRNA-p21* in aging pathologies remain to be investigated.

Increased expression of lncRNA *PINT*, another TP53-inducible lncRNA also named *lincRNA-Mkln1*, lowers caspase-3 and caspase-7 levels, while silencing *PINT* induces their abundance. *PINT* interacts with SUZ12, a component of the PRC2 complex involved in histone modification and transcriptional repression, thereby contributing to the repression of certain genes. *PINT* is upregulated in human colorectal cancer and is required for proliferation of the human cancer cell line HCT116, linking this stress-responsive lncRNA to tumor-associated gene regulation [180].

DNA damage also induces *PANDA* (p21-associated ncRNA DNA damage-activated) in a TP53-dependent manner [181]. In proliferating cells, *PANDA* recruits PRC1 and PRC2 complexes to repress transcription of pro-senescence PRC target genes, such as those that encode CDKN1A (p21) and *PANDA* itself. In senescent cells, PRC1 and PRC2 complexes dissociate and the levels of *PANDA* and CDKN1A increase; under these conditions, *PANDA* blocks proliferation by associating with NF-YA, while CDKN1A solidifies growth arrest by activating pRB. Accordingly, depletion of the lncRNA *PANDA* leads to exit from senescence [182].

Treatment with the radiomimetic drug and inducer of DNA damage neocarzinostatin (NCS) upregulated many lncRNAs, including *lncRNA-JADE* (located next to *JADE1*), in an ATM-dependent manner. *LncRNA-JADE* depletion inhibits JADE1 induction by NCS and sensitizes cells from NCS-induced apoptosis, while *lncRNA-JADE* overexpression promotes JADE1 expression and inhibits apoptosis. In addition, *LncRNA-JADE* interacts with the transcription co-activator BRCA1, a major player in cancer, senescence and aging [183,

184], supporting the notion that cancer cells may achieve resistance to apoptosis by modulating stress and ATM-dependent lncRNA expression.

LncRNA-LET is downregulated in cancers, as mentioned above, via transcriptional repression during hypoxia. Interaction of *lncRNA-LET* with the RBP NF90 promoted NF90 ubiquitination and degradation [44] and thus the hypoxia-lowered *lncRNA-LET* caused NF90 upregulation. Interestingly, overexpression of *lncRNA-LET* or depletion of NF90 suppressed HIF-1 α mRNA induction following hypoxia [44].

Other lncRNAs may also modulate TP53 expression under stress conditions. For instance, depletion of *lncRNA-ROR* enhances TP53 translation in the absence of stress, while its upregulation with stress or its ectopic expression suppresses TP53 translation through its direct interaction with the RBP hnRNP I. Interestingly, the promoter region of *lncRNA-ROR* contains TP53-binding sites and TP53 overexpression promotes *lncRNA-ROR* transcription, suggesting the existence of negative feedback regulation [185]. Finally, the expression levels of long stress-induced non-coding transcripts (LSINCTs) increase under stress conditions such as DNA damage. These lncRNAs are highly expressed in lung and breast cancer cell lines [186] and may rise in aging tissues, given that DNA damage accumulates with age.

3.3. lncRNAs affecting age-associated immune decline

Aberrant immune responses are a hallmark of aging and age-associated diseases, in part associated with the continuously secretion of proinflammatory cytokines by senescent cells [187, 188]. Recently, lncRNAs were reported to influence cytokine production and to modulate the subcellular localization of transcription factors involved in the cellular defense mechanisms against pathogenic and viral infections. The impact of lncRNAs on the immune response appears to be relatively well conserved across species [189]. Recent findings of lncRNAs linked to impaired immune responses in aging pathologies are detailed below.

Among the lncRNAs involved in the immune response, *lincRNA-Cox2* was found upregulated after treatment with LPS (lipopolysaccharide) or the Toll-like receptor (TLR2/TLR1) agonist Pam3CSK4 in bone marrow-derived macrophages (BMDM), and required the transcription factor NF κ B and the TLR adaptor Myd88. *lincRNA-Cox2* selectively repressed the transcription of immune genes via its interaction with the RBPs hnRNP A/B and hnRNP A2/B1, while it enhanced IL6 expression via TLRs [190]. These results demonstrate that *lincRNA-COX2* can activate and repress immune response genes in macrophages, and mediates the actions of NF κ B, a major player in aging and age-related diseases [191]. Expression of COX2 was elevated by the lncRNA PACER (p50-associated COX-2 extragenic RNA), which binds to p53, a repressive subunit of NF- κ B and blocks its association with the *COX2* gene promoter, facilitating the transcriptional upregulation of COX2 expression by NF- κ B [192].

The proinflammatory cytokine TNF α , linked to inflammation, aging, age-related diseases, and cellular senescence [193], induces the expression of several lncRNAs, including *Lethe*, a pseudogene-encoded lncRNA transcribed by NF κ B. Depletion of *Lethe* led to an upregulation of NFKBIA and NFKB2, suggesting that *Lethe* may act as a repressor of NF κ B activity. Accordingly, ectopic expression of *Lethe* repressed the induction of NF κ B targets

like *Il6*, *Sod2*, *Il8*, and *Nfkb1a* [194], further supporting the view that *Lethe* participates in negative feedback modulation of NF κ B target genes regulated by TNF α to prevent a sustained immune response. By contrast, lncRNA *THRIL* (TNF α - and hnRNP L-related immunoregulatory lncRNA) declined after TNF α treatment. After complexing with its binding partner hnRNP L, *THRIL* induced transcription of TNF α via its promoter [195]. These findings underscore the involvement of lncRNAs in networks regulated by NF κ B and TNF α , two major regulators of aging, age-associated disease, and immune responses.

Expression of *NEAT1* is induced by polyI:C. Depletion of *NEAT1* inhibits the rise in *IL8* and *CCL5* mRNAs upon polyI:C treatment, while ectopic expression of *NEAT1* is sufficient to induce *IL8* and *CCL5* expression without further stimuli. In addition, *NEAT1* binds SFPQ, a transcriptional repressor of the *IL8* gene. These data suggest that *NEAT1* induced by polyI:C or viral infection might sequester SFPQ from the *IL8* promoter region, activating *IL8* transcription in response to an immune stimulus [196]. A similar mechanism may contribute to upregulating *IL8* in the elderly, a process associated with cognitive dysfunction [197, 198].

Other lncRNAs tied less directly with aging include *lnc-DC*, which interacts with STAT3, a transcription factor closely implicated in the immune response, tumorigenesis and aging [199-201], and *NeST*, which controls Theiler's virus infection and resistance to *Salmonella* infection in mice by elevating transcription of the cytokine IFN γ [202]. *NeST* may participate in aging-associated processes through its impact on the expression of IFN γ , a cytokine closely linked to age-related diseases, and through Theiler's virus links to inflammation and neurological diseases [203-205].

4. AGING-ASSOCIATED NEURODEGENERATION

Neurodegenerative disorders in the elderly include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Amyotrophic lateral sclerosis (ALS). Recently, several articles reported the role of lncRNAs in this group of diseases, as well as in schizophrenia, spinocerebellar ataxia, sciatic nerve injury, and neurogenesis [206]. In this section we will discuss lncRNAs affecting age-related neurological diseases (Table 3).

BACE1-antisense transcript (*BACE1-AS*) has extensive complementarity with *BACE1* mRNA and enhances *BACE1* mRNA stability by protecting it from degradation by factors including miR-485-5p [207, 208]. BACE1 protein levels and activity increase with brain aging and AD; in AD, high BACE1 levels correlate with elevated *BACE1-AS* abundance, suggesting that *BACE1-AS* could play a role in AD development or progression [207, 209, 210].

Also highly abundant in individuals with AD, *lncRNA-17A* is associated with a defect in the alternative splicing of GABABR2 (γ -aminobutyric acid B receptor 2). Overexpression of *lncRNA-17A* repressed GABABR2 variant A, promoted expression of variant B, and favored the accumulation of peptides A β 42 and A β 40, derived from cleavage of the amyloid precursor protein (APP) and closely implicated in AD pathogenesis. These findings indicate that *lncRNA-17A* may play a role in GABA signaling and A β production [211]. Also in AD,

BCYRN1 was found to decrease by >60% in cortical areas between the ages of 49 and 86, but was upregulated in AD brains compared to age-matched normal brains [154].

The lncRNA *GOMAFU* (also known as *myocardial infarction-associated transcript*, *MIAT*) was downregulated in mouse cortical neurons and neurons derived from human induced pluripotent stem cell (iPSC) upon KCl-induced depolarization. *GOMAFU* interacts with QKI and SRSF1 to modulate the alternative splicing of *DISC1* and *ERBB4* pre-mRNAs, suggesting that by downregulating *GOMAFU*, potassium-activated ion channels make splicing factors available to carry out alternative splicing [212]. These could be linked to changes in alternative splicing of genes associated with age-related neurological disorders such as *DISC1*, for which some splice variants were associated with age-related recurrent major depression [213, 214].

Sciatic nerve injury led to differential expression of many lncRNAs, including *BC089918*, which was downregulated upon injury and its depletion promoted the outgrowth of dorsal root ganglion neurons. This function of *BC089918* in the recovery of neurons from sciatic nerve injury has potential relevance to nerve injury and recovery in the elderly [215].

Expression of the brain-specific lncRNA *RMST* (rhabdomyosarcoma 2-associated transcript), which is transcriptionally repressed by the neuronal transcription factor REST, is essential for neurogenesis. In neural cells, *RMST* associated with the transcription factor SOX2 and the complex was necessary for the recruitment of SOX2 to appropriate DNA regions to implement a neurogenic program. *RMST* also interacts with the hnRNP A2/B1, whose aberrant function is associated with neurodegeneration [216, 217].

As mentioned above, the lncRNA *GAS5* was associated both with cancer and with neurodegeneration, at least in part by acting as decoy for the transcription factor GR and thus inhibiting GR-driven gene expression programs and inducing apoptosis [30, 218, 219]. *Gas5* was recently found to be highly expressed in the hippocampus of aged mice and mice subject to psychogenic stress (stress triggered by behavioral or emotional factors). Higher levels of *Gas5* were associated with spatial-learning impairments and reduced novelty-induced exploration. These findings suggest a possible impact of lncRNA *GAS5* on age-related behavior impairment and stress-induced changes in hippocampal function [218].

5. CONCLUDING REMARKS AND PERSPECTIVES

Numerous diseases that arise with advancing age, including obesity, diabetes, frailty, cancer, and neurodegeneration, are characterized by altered patterns of expressed transcripts, both coding and noncoding. As discussed in this review, lncRNAs affecting aging pathologies can modulate protein profiles via transcriptional and posttranscriptional regulatory processes (Figure 1). Through this broad range of influences, lncRNAs can regulate age-associated disease processes at the cell, tissue, organ, and system levels. Indeed, a few animal models are beginning to emerge supporting roles for lncRNAs in aging physiology and pathology at the organism level. For example, mouse lncRNAs from the myosin heavy chain 7 (*Myh7*) loci were found to be cardioprotective [220], deletion of *Xist* in mouse hematopoietic cells caused blood cancers, highlighting a tumor suppressive function for *Xist* [221], and

knockdown of the neuronal lncRNA *tuna* in zebrafish recapitulated the impaired locomotor function seen in the brains of Huntington's disease patients [221].

It is therefore essential to understand comprehensively the spectrum of lncRNAs implicated in age-associated diseases, as well as the mechanisms that control lncRNA expression and localization. Given that their function is often linked to their interaction with other molecules, it is also critical to elucidate systematically the factors with which these lncRNAs interact: the proteins, DNA elements, mRNAs, microRNAs, and other noncoding RNAs that form complexes with lncRNAs. Not all lncRNAs are well conserved phylogenetically, but their structure and function does appear to be maintained with evolution [11, 223]. Therefore, assessment of these complexes in the context of the cell and the organism will provide valuable insight towards understanding the mechanisms of action of lncRNAs in aging pathologies.

lncRNAs are rapidly becoming molecules of exceptional interest in disease diagnosis and prognosis. The ease of detection of many lncRNAs in various bodily fluids, particularly blood, make this class of molecules attractive targets for different clinical applications; for example, *lncRNA-ROR* was recently found to be mobilized into extracellular vesicles, an event that was discovered to protect hepatocellular cancer against therapeutic interventions [224]. In addition, while lncRNAs are assumed not to produce large proteins, many lncRNAs are predicted to have short open reading frames that may give rise to small peptides that have thus been difficult to study. However, the development of better technical and computational methods [225] is facilitating the identification of micropeptides expressed from lncRNAs. One recent example is the skeletal muscle-specific micropeptide myoregulin (MLN), expressed from a 138-nucleotide open reading frame in an intron of a mouse lncRNA [226]. MLN was found to be a strong modulator of the muscle calcium system and thus modulated muscle contraction [226]; given its high conservation between mouse and human, MLN may be relevant to the decline in muscle function seen with human aging. Other lncRNA-encoded micropeptides of potential clinical interest are likely to emerge, as their analysis expands and deepens [227, 228].

With advances in our understanding of lncRNA expression and function, we can expect to identify classes of target lncRNAs of therapeutic interest that can be increased or suppressed for clinical benefit. At the same time, we are witnessing fast progress in technologies to detect aberrant lncRNAs and deliver lncRNA-relevant therapy with increasing precision and efficacy. In this regard, revolutionary advances in the design of adenoviral and AAV (adenoviral-associated) vectors for RNA delivery, the development of cell-specific RNA aptamer drugs, nanotechnology, and the widespread adoption of CRISPR (clustered regularly interspaced palindromic repeats)-Cas9-mediated interventions are enhancing our ability to repress and enhance gene expression with increasing accuracy. Thus, interventions to reduce the levels of harmful lncRNAs or elevate beneficial lncRNAs in selective tissues at specific times may soon become a reality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Long noncoding (lnc)RNAs regulate gene expression programs in aging pathologies
- LncRNAs govern aging-impaired energy metabolism (obesity, diabetes)
- LncRNAs affect aging-impaired proliferative and immune responses (cancer, immunity)
- LncRNAs modulate age-related neurodegeneration
- LncRNAs involved in diseases of aging represent promising therapeutic targets

Figure 1. Molecular mechanisms of action of lncRNAs implicated in age-associated diseases

In the nucleus, many lncRNAs involved in age-associated diseases elicit changes in chromatin or modulate the organization of chromosomes, control (enhance or repress) transcription by acting on transcription factors, or can modulate splicing by acting upon splicing regulatory factors. In the cytoplasm, lncRNAs implicated in age-associated diseases can modulate positively or negatively the stability or translation of subsets of mRNAs, alter the turnover of proteins, function as sponges/decoys for microRNAs or proteins, or influence mitochondrial metabolism.

Table 1

LncRNAs in aging-associated diabetes, obesity, mitochondrial disease, and muscle dysfunction

LncRNA	Processes	Targets	Relevance to Aging, Other Implications	Refs.
Obesity				
lnc-RAPs	Adipogenesis	(various)	Many lnc-RAPs induced by PPAR γ (a TF reduced with age) and C/EBP α	[55, 56]
<i>lnc-RAP-1</i> , <i>Firre</i>	Adipogenesis	genes <i>Slc25a12</i> , <i>Eef1a1</i> , <i>Atf4</i> , <i>Ppp1r10</i> (on chromosomes 2, 9, 15, 17), and hnRNP U	Helps organize nuclear architecture across chromosomes	[57]
<i>naPINK1</i>	Obesity, diabetes, neurodegeneration, muscle activity	<i>PINK1</i> mRNA, encoding a mitochondrial kinase	In inactive muscle, low <i>PINK1</i> mRNA and high <i>naPINK1</i> ; after endurance training, high <i>PINK1</i> mRNA and low <i>naPINK1</i>	[58-60]
<i>H19</i>	Fat deposition and fat metabolism	Imprinting of gene cluster that includes <i>IGF2</i>	High IGF2 and <i>H19</i> due to loss of imprinting during aging linked to fat deposition and cancer	[61, 62]
<i>linc-DMRT2</i>	Adipogenesis	Undetermined	Low in fat tissue of obese humans	[63]
<i>linc-TP53H13</i>	Adipogenesis	Undetermined	Low in fat tissue of obese humans	[63]
Diabetes				
<i>KCNQ1OT1</i>	Diabetes	Undetermined	High in pancreatic islets of diabetic individuals	[74]
<i>HI-LNC45</i>	Diabetes	Undetermined	Low in pancreatic islets of diabetic individuals	[74]
<i>HI-LNC78</i> , <i>HI-LNC80</i>	Sensing glucose levels	Undetermined	Elevated by high glucose	[74]
<i>HI-LNC25</i>	β cell function	<i>GLIS3</i> mRNA	β cell function in adults	[74, 75]
<i>ANRIL</i>	Proliferation capacity of β cells(?)	PRC1, PRC2, p16 ^{INK4A} and p15 ^{INK4B}	<i>ANRIL</i> identified as hotspot of T2D mutations, suppresses (via PRC1,2) transcription of tumor suppressors and senescence inducers p16 ^{INK4A} and p15 ^{INK4B}	[76-78]
Mitochondria				
<i>LNCND5</i> , <i>LNCND6</i> , <i>LNCCTB</i>	Mitochondrial gene regulation	Undetermined	Encoded by mitochondrial genome	[83-85]
<i>RMRP</i>	Mitochondria function	Undetermined	Encoded by nuclear genome	[86]
<i>LIPCAR</i>	Myocardial infarction	Undetermined	Encoded by mitochondrial genome, levels in blood have prognostic value	[88-91]

LncRNA	Processes	Targets	Relevance to Aging, Other Implications	Refs.
Muscle physiology				
<i>H19</i>	Skeletal muscle regeneration(?)	Suppresses BMP pathway, TFs SMAD1,5 replication factor CDC6	<i>H19</i> levels selectively upregulated in old muscle, hosts miR-675, which elicits some of <i>H19</i> actions	[92]
<i>linc-MD1</i>	Muscle regeneration and sarcopenia	Decoys miR-133 and miR-135	Decoys miR-133, alleviating repression of HuR/ELAVL1	[96-99]
<i>SIRT1 AS</i>	Myogenesis	Myoblast <i>Sirt1</i> mRNA	SIRT1 helps maintain a robust myogenic program, <i>SIRT1 AS</i> prevents this	[100-102]
<i>MALAT1</i>	Myoblast proliferation	SRSF1, SRSF2, hnRNP C, TP53	<i>MALAT1</i> levels reduced by Myostatin, showing deficiency with age	[103-105]
<i>Yam-1</i>	Repression of myogenesis	Wnt7b Yam-1 harbors miR-715	TF YY1 (implicated in muscle wasting, cancer, diabetes, chronic heart failure) promotes Yam-1 expression	[107-108]

LncRNAs involved in aging-related decline in energy metabolism (column 1), the age-associated diseases and disease processes in which they are implicated (column 2), the direct molecular targets of the lncRNAs (column 3), and the relevance of the lncRNAs to energy metabolism and aging processes (column 4) are listed.

Table 2

LncRNAs in aging-associated cancer, stress susceptibility, and immune dysfunction

LncRNA	Processes	Targets	Relevance to Aging, Other Implications	Refs.
Cancer				
<i>H19</i>	Cancer, apoptosis, proliferation, aging	<i>IGF2</i> , many proliferation genes	<i>Igf2/H19</i> imprinting lost with aging, <i>H19</i> and its host, miR-675, elevated with aging and cancer; upregulated by MYC	[120-126]
<i>MEG3</i>	Growth inhibition	MDM2	<i>MEG3</i> overexpression lowers cancer cell growth, <i>MEG3</i> silencing promotes it	[127-132]
<i>MALAT1</i>	Cancer, senescence	TP53, SRSF1, SRSF2, hnRNP C	SP factors relevant to aging, senescence; High MALAT1 in lung and liver cancers	[133-138]
<i>ANRIL</i>	Cancer, senescence	p16 ^{INK4A} and p15 ^{INK4B} , PRC1, PRC2	Represses p16 ^{INK4A} and p15 ^{INK4B} , p21, KLF2; pro-tumorigenic in prostate and liver by silencing miR-449a and miR-99a	[140-144]
<i>HOTAIR</i>	Cancer, senescence	ubiquitin/proteolysis factors, PRC2	Prognostic in colorectal, cervical and endometrial carcinomas	[16,146-149]
<i>XIST</i>	Cancer, senescence	X chromosome	Prognostic in ovarian cancer chemotherapy	[151-153]
<i>BCYRN1</i>	Cancer, neurodegeneration	Undetermined	Decreased in brain of old individuals, highly expressed in numerous cancers	[154-156]
<i>GAS5</i>	Growth inhibition	Glucocorticoid Receptor	Decreased in breast and liver cancers	[157, 158]
<i>MIR31HG</i>	Senescence	miR-31 targets	Harbors miR-31 (down in ovarian cancer and leukemia)	[159-164]
<i>7SL</i>	Prevents autophagy and senescence	Binds to <i>TP53</i> mRNA in competition with HuR	Protumorigenic by lowering p53	[17, 43, 155]
<i>HULC</i>	Tumorigenesis		Liver and colon cancer	[166, 167]
<i>lncRNA-LET</i>	Tumor suppression	Binds, destabilizes NF90	Downregulated by hypoxia and HIF-1α; modulates NF-90-governed SASP	[44, 168]
<i>PCGEM1</i>	Anti-apoptosis	Undetermined (indirectly TP53, p21, others)	Promotes prostate cancer cell survival after chemotherapy	[169, 170]
<i>PVT1</i>	Anti-apoptosis, growth inhibition	Undetermined	Upregulated by MYC; prognostic of response to chemotherapy	[171, 172]
Stress Response				
<i>lincRNA-p21</i>	Response to DNA damage, hypoxia	<i>CTNNB</i> mRNA, <i>JUNB</i> mRNA	Induced by TP53 and hypoxia, implicated in senescence and growth arrest	[176, 179]
<i>PINT</i>	DNA damage, tumor suppression	SUZ12, epigenetic silencing by PRC2	Induced by TP53, reduces proliferation, low in colon cancer	[180]
<i>PANDA</i>	Cell proliferation,	PRC1, PRC2	Interacts with PRC1,2 in dividing cells,	[181]

LncRNA	Processes	Targets	Relevance to Aging, Other Implications	Refs.
	growth inhibition		represses p21 and growth inhibitory genes; released from PRC1,2 in senescent cells	
<i>lncRNA-JADE</i>	DNA damage	BRCA1	Upregulated via ATM, activates JADE1 transcriptionally	[183, 184]
<i>lncRNA-LET</i>	Hypoxic stress	Binds, destabilizes NF90	Downregulated by hypoxia and HIF-1 α ; modulates NF-90-governed SASP	[44]
<i>lncRNA-ROR</i>	DNA damage	hnRNP I	Represses TP53 translation	[185]
LSINCTs	DNA damage	Undetermined	Highly expressed in lung and breast cancer	[186]
Immune Response				
<i>lincRNA-Cox2</i>	Immune response	hnRNP A/B, hnRNP A2/B1	Upregulated by LPS and Pam3CSK4 in macrophages, linked to NF- κ B function	[190, 191]
<i>Lethe</i>	Induced by TNF α	Undetermined	Pseudogene-encoded lncRNA transcribed by NF κ B, represses NF κ B target genes	[193]
<i>THRIL</i>	Repressed by TNF α	hnRNP L	Induced TNF α transcriptionally	[194]
<i>NEAT1</i>	Viral infection	SFPQ	Induces IL8, linked to cognitive loss	[195-197]
<i>lnc-DC</i>	Immune response	STAT3	Implicated in tumorigenesis, aging	[198-200]
<i>NeST</i>	Viral infection	Undetermined	Inflammation, neurological disease	[201-204]

LncRNAs involved in aging-related decline in body homeostasis (column 1), the age-associated disease processes in which they are implicated (column 2), the direct molecular targets of the lncRNAs (column 3), and the relevance of the lncRNAs to homeostatic processes (column 4) are listed.

Table 3

LncRNAs in aging-associated neurodegeneration.

LncRNA	Processes	Targets	Relevance to Aging, Other Implications	Refs.
<i>BACE1AS</i>	AD	<i>BACE1</i> mRNA, HuD	Competes with miR-485-5p for binding to, and repressing <i>BACE1</i> mRNA	[207-210]
<i>lncRNA-17A</i>	AD	Modulates alternative splicing of <i>GABABR2</i> pre-mRNA	Repressed GABABR2 variant A, promoted variant B, and enhanced accumulation of peptides A β 42 and A β 40	[211]
<i>BCYRN1</i>	AD	Undetermined	Upregulated in AD brain cortex	[154]
<i>GOMAFU (MIAT)</i>		QKI and SRSF1	Modulates alternative splicing of <i>DISC1</i> (linked to age-related neurological disorder), and <i>ERBB4</i> pre-mRNAs	[212-214]
<i>BC089918</i>	Sciatic nerve injury	Undetermined	Downregulated in elderly, proposed as cause of impaired nerve injury, recovery	[215]
<i>RMST</i>	Neurogenesis, neurodegeneration	hnRNP A2/B1, SOX2	Transcriptionally repressed by REST, <i>RMST</i> is essential for neurogenesis	[216, 217]
<i>GAS5</i>	Neurodegeneration, cancer	GR decoy	Induced by psychogenic stress in hippocampus of aged mouse, linked to impaired learning and exploration	[30, 218, 219]

LncRNAs involved in neurodegeneration (column 1), the specific disease processes in which they are implicated (column 2), the direct molecular targets (column 3), and the relevance of the lncRNAs to neurodegeneration and aging-relevant events (column 4) are listed.