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Noncoding RNA Control of Cellular Senescence

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Abstract

Senescent cells accumulate in normal tissues with advancing age and arise by long-term culture of primary cells. Senescence develops following exposure to a range of stress-causing agents and broadly influences the physiology and pathology of tissues, organs, and systems in the body. While many proteins are known to control senescence, numerous noncoding (nc)RNAs are also found to promote or repress the senescent phenotype. Here, we review the regulatory ncRNAs (primarily microRNAs and lncRNAs) identified to-date as key modulators of senescence. We highlight the major senescent pathways (p53/p21 and pRB/p16), as well as the senescence-associated secretory phenotype (SASP) and other senescence-associated events governed by ncRNAs, and discuss the importance of understanding comprehensively the ncRNAs implicated in cell senescence.

Keywords

chromatin remodeling; long noncoding RNA; microRNA; mRNA stability; mRNA translation; post-transcriptional gene regulation; SASP; ribonucleoprotein complexes; transcriptional gene regulation; transcriptome

INTRODUCTION

Cell senescence

First described by Hayflick 1965, senescence is a property of nontransformed cells whereby they divide for a limited number of times before they cease to proliferate and acquire a state of long-term arrest.[1] Cellular senescence has been studied most extensively in cultured primary cells, where it is triggered with different kinetics by a variety of factors.[2]

Replicative senescence arises from a critical loss in the length of telomeres, the structures at the ends of chromosomes that provide protection for proliferating cells and enable DNA polymerase to complete replication.[2] Accordingly, replicative senescence can be delayed by restoring the expression of telomerase, the enzyme that replenishes telomeres.[3] Critically short telomeres initiate the DNA damage response (DDR), characterized by the presence of DNA nuclear foci enriched in DDR proteins such as γ-H2AX and by elevated expression of the tumor suppressor protein p53 and its transcriptional targets p21 [an inhibitor of cyclin-

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dependent kinases (CDKs)] and ARF.[4,5] Together, the p53/p21/ARF axis inhibits the cell replication machinery and potently induces growth arrest. Replicative senescence is also controlled by the tumor suppressor protein retinoblastoma (pRB). pRB and its activator, the cdk inhibitor p16 (INK4A), constitute the second major axis of senescence regulation and repress the replication of somatic and stem cells by blocking the cell division cycle.[4,5] In fact, $p16^{INK4A}$ alone can suppress stem cell self-renewal and proliferation of somatic cells. Another halmark feature of senescence is the senescence-associated secretory phenotype (SASP), whereby senescent cells express and secrete cytokines, growth factors, and extracellular matrix (ECM)-remodeling enzymes.[6]

Premature senescence is not elicited by shortened telomeres, although it is also established and maintained by the two major senescence-regulatory pathways, p53/p21 and pRB/p16. Exposure to stresses such as oxidants, radiation, heat, toxins, or chemotherapeutic agents can trigger premature senescence through activation of the DDR that culminate in growth arrest by cdk inhibitors and heterochromatin changes.[2] Premature senescence can also arise from the unscheduled activation of oncoproteins like K-RAS V12 and BRAF V600E or from the inactivation of tumor suppressor proteins such as NF1, VHL, and PTEN.[5,7,8] SASP is also observed during premature senescence.[6]

Senescence in physiology and pathology

Numerous studies over the past decade have shown that the accumulation of senescent cells in tissues *in vivo* can have both positive and negative consequences The health-promoting impact of senescent cells is well recognized in a number of conditions, often in young organisms. In young persons, senescence is widely considered to be a tumor suppressive mechanism, a way to impede the propagation of cells bearing damaged DNA with potentially malignant mutations.[4] By inhibiting their growth and activating tumor suppressors p53, pRB, and p16, senescence can suppress tumorigenesis. Similarly, activation of oncogenes (e.g., K-RAS V12 or BRAF V600E) induces senescence in a variety of malignancies[9-11] and inactivation of tumor suppressors (e.g., NF1, VHL, PTEN, SKP2) can promote senescence *in vivo.*[12-14] Another beneficial effect of senescence is the suppression of tissue fibrosis and liver damage. Activation of hepatic stellate cells (HSCs) by tissue damage leads to hyperproliferation and cell senescence, which reduces the secretion of extracellular matrix proteins and increases the secretion of ECM-degrading proteins, limiting liver fibrosis.[15] Similarly, repair of pancreatic tissue damage is favored by senescent stellate cells limiting pancreatic fibrogenesis.[16] Senescence is also involved in the skin wound healing process. Senescent skin fibroblast secrete CCN1 also known as CYR61 (Cysteine-rich angiogenic inducer 61). CCN1 induces DNA damage, p53 activation, and enhanced expression of anti-fibrotic genes leading to restrict fibrosis in cutaneous wound healing.[17,18] Additionally, senescent cells secrete numerous inflammatory cytokines (the trait SASP mentioned above). In response to a cutaneous wound in a mouse model, senescent fibroblasts and endothelial cells appear very early to accelerate the healing process by secretion of platelet-derived growth factor AA (PDGF-AA).[19] During muscle repair in young animals, quiescent satellite cells are activated to initiate proliferation and myogenic differentiation.[19]

On the other hand, numerous detrimental actions of senescent cells have been observed in the context of age-related conditions, including cancer, cardiovascular diseases, neurodegeneration, diabetes, sarcopenia, and declining immune function in the elderly.[4,20-23] For instance, in older persons, senescent cells can contribute to tumorigenesis of neighboring cells through the secretion of oncogenic factors such as interleukin (IL)-6, IL-8, IL-1α, granulocyte-macrophage colony stimulating factor (GM-CSF), the growth-regulated oncogene α (GROa), monocyte chemotactic protein (MCP)-2, MCP-3, matrix metalloprotease (MMP)-1, MMP-3, and many insulin-like growth factor (IGF)-binding proteins.[22,24] This secretory program can support malignancy and was shown to enhance oncogenesis of cancer cells co-cultured with senescent fibroblasts.[25] Besides carcinogenesis, senescence can have detrimental impact on other aging-associated pathologies. For instance, senescent cells accumulate in Parkinson's and Alzheimer's diseases, and impair vascularization in diabetes.[26,27] Senescence of skeletal muscle cell and satellite cells has also been linked to the age-related muscle disorder sarcopenia. In mouse muscle, satellite cells derepress p16 in order to become senescent;[28,29] accordingly, mice lacking p16 are partially protected from age-related reduction in the self-renewal of neuronal progenitors, and enhance islet proliferation and regeneration.[30,31] Finally, immunosenescence enhances the age-related decline in the adaptive immune system.[32]

Given the impact of senescence on human physiology and pathology, in-depth understanding of the molecular regulators of senescence will enable us to target this process for therapy, whether the goal is to enhance it or to reduce it.

Assessment of senescence

Senescent cells can be identified by assessing certain phenotypic traits. Replicative senescence causes cells to adopt a flat and enlarged morphology that can be observed using regular microscopy.[33] Senescent cells are also easily detected by the presence of a senescence-associated β-galactosidase (SA-β-gal) activity.[34,35] In addition, they express certain patterns of RNAs (coding and noncoding) as well as proteins;[36-38] these patterns can be assessed by various methods including quantitative PCR, gene array, or RNA sequencing analyses. Global translation and global protein turnover are also altered in senescent cells, further contributing to differences in their proteome profile as compared with young cells. These changes in protein expression patterns (especially the rise in expression of cdk inhibitors) contribute to a growth-inhibited state that can be assessed by flow cytometry or by measuring *de novo* thymidine incorporation. In addition, senescent cells exhibit the trait SASP, which elicits important changes in the microenvironment and in distant tissues, and can be detected by Western blot analysis or ELISA.[39-41] Finally, senescent cells are characterized by the presence of altered chromatin structure and DNA damage accompanied by detectable senescence-associated heterochromatic foci (SAHF) and H2AX phosphorylated on serine 139 (γ-H2AX).[42,43] These markers can be used to detect senescence in cultured cells and *in vivo*. It is important to employ more than one method in order to identify senescent cells without ambiguity (for instance, by assessing SA-β-gal activity, cell proliferation, and DDR protein levels).[35,44,45]

NONCODING RNA

microRNAs

microRNAs are transcribed as long transcripts (primary or pri-microRNAs) by RNA polymerases II and III, and then processed into microRNA precursors (pre-microRNAs) by a microprocessor complex that includes the ribonuclease Drosha and DiGeorge critical region 8 (DGCR8) protein.[46-49] Following export to the cytoplasm by exportin 5, pre-microRNAs are cleaved by Dicer to form the mature microRNA, which is loaded into the RNA-inducible silencing complex (RISC).[48,49] These complexes target specific mRNAs (mainly in the 3'UTR) through partial complementarity, often with extensive matching at the 'seed' region, and lower the stability and/or translation of the target mRNA.[50,51]

Long noncoding RNAs (lncRNAs)

LncRNAs are transcripts that lack protein-coding capacity. Their size ranges from ~200 bases to hundreds of kilobases. LncRNAs transcribed from the vicinity of a protein-coding gene can be transcribed in the sense or antisense direction relative to the reference mRNA. LncRNAs can also be transcribed from intronic or intergenic regions and can arise from mutations in mRNAs, from chromosomal rearrangements, and from transposon insertions.[52,53]

LncRNAs can regulate gene expression through interaction with chromatin modifiers, DNA, RNA, and RNA-binding proteins (RBPs).[54-58] They can modulate transcription by influencing the organization of chromatin and nuclear speckles, and by controlling RNA polymerase II initiation through the recruitment of transcriptional activators or repressors.[59,60] LncRNAs can also regulate gene expression post-transcriptionally at many levels; through their interaction with RNA and proteins, they can modulate pre-mRNA splicing, mRNA stability, protein translation, and protein stability .[61-65] Additionally, lncRNAs can act as 'decoys' or 'sponges' for factors such as microRNAs and RBPs, thereby modulating the impact of these factors upon target mRNAs.[66,67] At the post-translational level, some lncRNAs can function as molecular scaffolds to facilitate the assembly of multi-protein complexes.[66] Circular RNAs (circRNAs) are a highly stable subclass of lncRNAs due to the absence of 5' and 3' ends. They can regulate gene expression programs at least in part by serving as sponges for specific microRNAs.[68,69] Their involvement in senescence is under intense investigation (unpublished results) but has not yet been reported.

The expression of many ncRNAs has been found to change with senescence.[23,70,71] Here, we review studies on the main ncRNAs implicated in senescence. We discuss the best-studied senescence-associated microRNAs (SA-microRNAs) and senescence-associated long noncoding RNAs (SAL-RNAs) implicated in promoting or suppressing cell senescence by focusing on the specific senescence pathways[2,5,6] in which they are involved (Figure 1, Tables 1-3).

ncRNAs IMPLICATED IN THE p53/p21 SENESCENCE PATHWAY

The tumor suppressor and senescence marker protein p53 activates a transcriptional program associated with cell cycle progression and senescence which prominently includes p21

upregulation. Several ncRNAs have been identified as regulators of p53 expression, and reciprocally p53 can regulate the expression of many ncRNAs that play major roles in pro-senescence networks (Fig. 1, Table 1).

SA-microRNAs in the p53/p21 pathway

p53 is a key inducer of microRNAs in the miR-34 family.[72] In turn, miR-34a promotes senescence of endothelial cells and colon cancer cells by targeting the E2F pathway.[73] miR-34a can also induce senescence at least in part by preventing expression of SIRT1 (silent mating type information regulator 2 homolog 1), a protein that has a complex impact upon senescence. Since SIRT1 inhibits endothelial progenitor cell senescence, miR-34a abolishes this inhibition and restores senescence.[74] SIRT1 expression is also repressed by other microRNAs that induce senescence, such as miR-22 and miR-217,[75-77] while the p53 homolog ΔNp63 suppresses transcription of three microRNAs that repress SIRT1, miR-138, miR-181a, and miR-181b, and thus ΔNp63 promotes proliferation.[78] miR-34 can also target other transcripts that are essential for cell growth, proliferation and survival, such as those encoding BCL2, E2F3 and MYC.[79] Expression of let-7 family members also increases during senescence.[80,81] Let-7 promotes senescence by lowering the production of proteins essential for proliferation such as EZH2, a suppressor of senescence in primary mouse embryonic fibroblasts (MEFs), and HMGA2.[82-85] Another transcriptional target of p53, miR-200c, increases following oxidative stress and triggers endothelial cell apoptosis and senescence; these effects were linked to miR-200c-mediated repression of the transcription factor and senescence-suppressor ZEB1.[86]

Some microRNAs directly target the 3'UTR of *p53* mRNA, including miR-25 and miR-30d, and thereby reduce the expression of p53 and p53-transcribed genes, as well as inhibit p53-mediated effects on cell survival and senescence.[87] On the other hand, miR-885-p targets and represses the production of CDK2 and minichromosome maintenance complex component 5 (MCM5), which allows p53 to accumulate, elevates p53-transcribed genes, and triggers neuroblastoma cell senescence.[88] In both HeLa cells and WI-38 fibroblasts, miR-519 reduces the expression of proteins essential for DNA repair and calcium homeostasis (ORAI1 and ATP2C1), triggering a stress response that elevates expression of p53 and p21 and leads to cell senescence.[71,89,90] Doxorubicin-induced senescence increases the expression of p21 by lowering the levels of the miR-106b~25 cluster (miR-106b, miR-93 and miR-25), suggesting a broader impact of this cluster in suppressing senescence.[91] Enhanced expression of p21 in oxidative stress-induced premature senescence is antagonized by miR-106a.[92] In this regard, oncogenic Ras(G12V)-mediated senescence requires p21, and this induction of senescence is prevented by miR-106b, while the oncogenic microRNA cluster miR-17~92 disrupts senescence and enhances oncogenic transformation by lowering p21 levels.[93,94] p21 is also the target of multiple senescence-inhibitory microRNAs such as miR-130b, miR-302a, miR-302b, miR302c, miR-302d, and miR-515-3p.[93]

SAL-RNAs affecting the p53/p21 pathway

Expression of the lncRNA *MEG3* is lost in several human cancer cell lines due to gene deletion or hypermethylation. Ectopic expression of *MEG3* in a number of cancer cells

inhibits growth, indicating that *MEG3* may act as a tumor suppressor lncRNA.[95] *MEG3* suppresses the expression of MDM2, a protein that prevents p53 accumulation by enhancing p53 ubiquitin-mediated degradation.[96] Elevated levels of *MEG3* can promote senescence, as seen in cervical cancer cells, and enhances expression of NR4A3 (nuclear receptor subfamily 4A3) in senescent cells.[97,98]

The lncRNA *Gadd7* regulates cell proliferation in rodent cells exposed to UV irradiation.[99] It interacts with TDP-43, disrupting TDP-43-*Cdk6* mRNA interaction, which causes destabilization of the *Cdk6* mRNA and lowers the production of CDK6, a protein necessary for increasing division and preventing senescence; however, a direct role of *Gadd7* in senescence has not yet been reported.[100,101] Human *lncRNA-p21* interacts with *CTNNB* and *JUNB* mRNAs with partial complementarity and suppresses translation of β-catenin and JunB, respectively.[62] Although *lncRNA-p21* has not yet been shown to influence senescence directly, it is transcriptionally induced by p53, rises in senescent cells, and represses translation of two proteins, β-catenin and JunB, which promote proliferation.[102-104] Another p53-induced lncRNA, *PINT*, interacts with polycomb repressor complex (PRC)2 to regulate the expression of proteins involved in senescence-relevant pathways controlled by TGF-β and p53.[105-107]

The lncRNA *7SL* forms the cytoplasmic ribonucleoprotein (RNP) complex known as SRP (signal recognition particle), necessary for insertion of secretory proteins into the lumen of the endoplasmic reticulum.[108] *7SL* is highly expressed in several cancers,[109] and suppresses *p53* mRNA translation by competing with the RBP HuR for binding to the *p53* 3'UTR. Conversely, downregulation of *7SL* enhances autophagy and senescence by enhancing p53 production.[63]

ncRNAs IMPLICATED IN THE pRB/p16 SENESCENCE PATHWAY

The anti-proliferative program elicited by pRB and p16 prominently involves inhibition of CDKs as well as transcription factors in the E2F family (Fig. 1, Table 2).

SA-microRNAs in the pRB/p16 pathway

Translation of p16 was repressed by miR-24 in human cervical carcinoma cells and diploid fibroblasts.[110] A negative correlation between miR-24 and p16 in senescent cells was reported in osteoarthritis-associated senescence, where miR-24 levels were reduced while p16 levels were elevated,[111] although miR-24 itself has not been reported to delay senescence. The abundance of p16 is indirectly upregulated by SA-microRNAs miR-26b, miR-181a, miR-210 and miR-424, through their joint repression of proteins chromobox (CBX)7, embryonic ectoderm development (EED), enhancer of zeste homologue (EZH)2 and suppressor of zeste 12 (Suz12). Interestingly, depletion of p16 suppresses this SA-microRNA program, suggesting the existence of a negative regulatory feedback loop.[112] Also within the p16-pRB pathway are four microRNAs shown to target *MKK4* mRNA and reduce MKK4 expression, miR-15b, miR-24, miR-25, miR-141, which showed reduced abundance in senescent fibroblasts concomitant with a rise in MKK4 levels. Overexpressing these microRNAs lowered p16 production and delayed WI-38 fibroblast senescence, while the joint reduction of these microRNAs increased MKK4 levels, activated p38, elevated p16

abundance, and accelerated the senescent phenotype.[113] In addition, miR-128a promotes cell senescence by reducing the levels of BMI1, a repressor of p16.[114]

SAL-RNAs in the pRB/p16 pathway

The lncRNA *ANRIL* (also known as *CDKN2B-AS1* and *p15AS*) is transcribed from the same locus as the *INK4b/ARF/INK4a* genes, but in opposite direction.[115] *ANRIL* regulates cell cycle progression at least in part by recruiting CBX7, a protein component of PRC1 which increases H3K27 methylation and thereby suppresses *INK4a* transcription. Interestingly, CBX7 variants with point mutations that disrupt binding to RNA or to methylated H3K27 repress genes in the *INK4A* locus, impairing cellular senescence.[116] *ANRIL* downregulation elevates cdk inhibitors p14, p15 and p16, further supporting the view that *ANRIL* represses cellular senescence. Accordingly, *ANRIL* levels are low in senescent WI-38 cells and *ANRIL* knockdown in cancer cells display reduced proliferation,[117-120]. In sum, by repressing the production of cdk inhibitors, *ANRIL* enhances proliferation and suppresses senescence.

The expression levels of lncRNA *vlincRNA* (very long intergenic ncRNA or *VAD*) increase during oncogene-induced human senescence and is required for the maintenance of senescence. *vlincRNA* activates gene expression of cell cycle inhibitors at the *INK4* locus by inhibiting the binding of the repressor H2A.Z to the *INK4* locus, and thus promotes cellular senescence.[121]

The mitochondrial DNA-encoded lncRNA *ASncmtRNA-2* (antisense noncoding mitochondrial RNA-2) was found elevated in senescent endothelial cells. This increase was accompanied by enhanced expression of p16. *ASncmtRNA-2* is a precursor transcript for two microRNAs that are elevated in senescent cells, miR-4485 and miR-1973.[122] These RNAs exemplify a lncRNA-microRNA interplay in cellular senescence, but it is not clear at present if the microRNAs are effectors of *ASncmtRNA-2*-induced senescence.

ncRNAs IMPLICATED IN SASP AND OTHER SENESCENCE PROCESSES

SASP ncRNAs

As mentioned above, senescent cells constitutively secrete inflammatory mediators (growth factors, ECM-degrading enzymes, and cytokines), a trait known as SASP (Fig. 1, Table 3).[40] IL-1β lowers the levels of miR-24, a repressor of *p16/INK4A* mRNA translation, leading to a rise in p16 levels.[111] miR-146a/b lowers the production of IL-1 receptor-associated kinase 1 (IRAK1).[123] Conversely, suppression of miR-146a/b elevates IRAK1 activity, which in turn activates the transcription factor NF-κB, causing transcriptional induction of IL-6 and IL-8, which further amplifies the impact of this microRNA on SASP. Interestingly, IRAK1 increases miR-146a/b levels, suggesting the presence of a negative feedback mechanism for fine-tuning SASP.[124] Oxidative stress-induced senescence increases the levels of miR-183, which in turn suppresses production of the SASP factor and senescence regulator integrin β1 (ITGB1).[125]

Extracellular microRNAs present in body fluids may interfere with the production of SASP factors by regulating Toll-like receptors (TLRs). For instance, let-7 binds and activates TLR7, while miR-21 binds and activates TLR7 in mice and TLR8 in human

macrophages[126,127]. In addition, IκB kinases are repressed by miR-155 and miR-199a in a variety of cell types, in turn suppressing NF-κB activation; these and other microRNAs involved in SASP and aging-associated inflammation were recently reviewed.[123]

The lncRNA *H19* is involved in cell proliferation and survival.[128-131] It regulates imprinting of the insulin-like growth factor 2 (*Igf2*) locus, maintaining adult hematopoietic stem cell quiescence,[132], although a direct link to SASP has not been established.

ncRNAs involved in telomere metabolism

Senescence is associated with a gradual shortening of telomere length.[2] The length of telomeres is regulated by the telomerase ribonucleoprotein complex that contains the protein TERT and two noncoding RNAs, *TERC* and *TERRA*. *TERC* contributes directly to maintaining telomere length and preventing premature senescence and aging, as observed in *TERC*-deficient mice.[133] *TERC* functions as a template for telomeric repeats and also as a scaffold to assemble protein components of the telomerase complex.[134-137] Mammalian *TERRA* ncRNAs vary in length between 100 and >9000 nt. The family of *TERRA* ncRNAs suppresses telomere elongation because *TERRA* contain several copies of the telomere UUAGGG repeat,[138] and thus constitute high-affinity ligands (and hence competitive inhibitors) for TERT.[139,140] Abnormal expression of *TERRA* ncRNAs induces premature senescence in fibroblasts due to the suppression of telomere elongation.[141] *TERRA* also participate in the removal of 3'G overhangs of uncapped telomeres during DNA damage-induced senescence and protect telomere ends.[142,143]

ncRNAs influencing other senescence traits

Several other microRNAs have been reported to induce senescence by targeting various transcription factors (Fig. 1). For instance, miR-29 and miR-30 reduce production of the transcription factor B-MYB, thereby preventing expression of proliferative proteins and enhancing senescence.[144] In melanoma cells, miR-203 induces senescence by reducing the production of E2F3A and E2F3B, two transcription factors involved in cell division, DNA repair and senescence, while miR-205 suppresses E2F1 and E2F5 production and induces senescence.[145-147] The tumor suppressor miR-22 is upregulated during cardiac aging, enhances senescence in cardiac fibroblasts, and inhibits cell growth by lowering expression of the epidermal growth factor receptor ERBB3 in lung carcinoma cells.[148,149]

Other microRNAs can also help trigger senescence by negatively regulating oncogene-encoding transcripts. For instance, miR-20a represses the proto-oncogene LRF (leukemia/lymphoma-related factor), a known transcriptional repressor of $p19^{ARF}$; consequently, miR-20a upregulates $p19^{ARF}$ expression and promotes senescence of mouse embryonic fibroblasts.[150] In keratinocytes, miR-191 reduces SATB1 and CDK6 expression, thereby inhibiting cell growth and inducing senescence.[151] miR-449a induces pRB-dependent cell cycle arrest and senescence by targeting cyclin D1 in prostate cancer cells.[152] Overexpression of miR-152 and miR-181a in senescent human dermal fibroblasts is sufficient to induce senescence, associated with reduced levels of adhesion proteins integrin α5 and collagen XVI.[153] MicroRNAs miR-186, miR-216b, miR-337-3p, and miR-760 jointly reduce expression of the α subunit of protein kinase CKII to induce senescence in

human colorectal cancer cells.[154] miR-494 reduces the levels of hnRNPA3, hnRNPQ, protein disulfide isomerase A3 (PDIA3), and UV excision repair protein RAD23 homolog B (RAD23B), and triggers senescence in lung cancer cells and diploid fibroblasts.[155,156] OncomiRs miR-372, miR-373, and miR-214 prevent cancer cell senescence;[157-158] in light of the fact that a rise in miR-214 reduced the efficacy of radiotherapy, knockdown of microRNA-214 in radioresistant lung cancer cells sensitized them to radiotherapy and stimulated senescence.[158]

The lncRNA *UCA1* (urothelial cancer-associated 1) enhances tumorigenesis of bladder and breast cancer cells.[159-161] However, in untransformed proliferating cells, *UCA1* is negatively regulated by the CAPERα/TBX3 protein complex.[162] Oncogenic stress triggers CAPERα/TBX3 dissociation from *UCA1*, leading to its accumulation and the onset of senescence and suggesting a role for *UCA1* in oncogene-induced senescence. In agreement with this possibility, *UCA1* is induced in RAS-triggered senescence, *UCA1* overexpression is sufficient to trigger senescence, and silencing *UCA1* delayed senescence.[162] While these findings connect *UCA1* with RAS-induced senescence, the molecular mechanisms responsible for these actions have not been reported.

Similar to *UCA1*, the lncRNA *PANDA* may also either promote or suppress senescence depending on the specific interacting factors. In proliferating cells, *PANDA* interacts with SAFA (scaffold-attachment-factor A) and PRC; the SAFA-*PANDA*-PRC complex suppresses the transcription of genes that promote senescence and thus induces senescence. In senescent cells, on the other hand, *PANDA* binds the transcription factors NF-YA and E2F and reduces the transcription of proliferative genes. Together, these findings indicate that *PANDA* can modulate both the triggering and the prevention of senescence.[163]

Another lncRNA showing reduced levels in senescent cells is *MALAT1*.[117,164] Downregulation of *MALAT1* in young proliferating cells and in human cervical cancer cells induced cell cycle arrest, enhanced cellular senescence, and reduced tumor size, at least in part by regulating the levels of the oncogenic transcription factor B-MYB.[117,164-166] These findings indicate that *MALAT1* may be essential for proliferation. Although *MALAT1* is not essential for development,[167] its impact upon pathological or environmental challenges has not been studied in depth at present.

The lncRNA *HOTAIR* (HOX transcript antisense RNA) interacts with the repressor complex PRC2 leading to silencing of the *HOXD* locus.[168] Elevated in senescent fibroblasts, *HOTAIR* functions as a scaffold RNA molecule in the cytoplasm, serving as a substrate for E3 ubiquitin ligases and promoting the ubiquitination and subsequent degradation of Ataxin-1 and Snurportin-1. *HOTAIR* promotes cellular senescence, since silencing *HOTAIR* reduced the accumulation of senescent HeLa cells in a model of senescence triggered by HuR silencing.[169]

XIST, a lncRNA responsible for imprinting and hence silencing of the X chromosome in females (to compensate for the dosage effect in males),[170,171] displays lower levels in senescent cells.[117] However, its specific function in senescence has not been described yet.

CONCLUSIONS AND PERSPECTIVES

Senescent cells accumulate in tissues with advancing age and exposure to stress stimuli, having both beneficial and detrimental influences upon tissue homeostasis, as described above. Beneficial effects of senescence include tumor suppression and muscle regeneration in young organisms, prevention of liver and pancreatic fibrosis, and skin wound healing. Detrimental effects of senescence have been reported in cancer, cardiovascular diseases, neurodegeneration, diabetes, sarcopenia, and declining immune function. Given the impact of senescence in human health and disease, there is escalating interest in elucidating the molecular regulators of senescence in order to intervene therapeutically to accelerate or prevent senescence. Towards this goal, one of the immediate challenges is to determine whether ncRNAs that modulate cell senescence in culture also influence cell senescence in the organism and can influence physiology and pathology. In this regard, it will be particularly important to establish whether the impact of SA-ncRNAs changes with organismal age.

As reviewed here, ncRNAs of different sizes and types can influence cellular senescence. A growing number of microRNAs and lncRNAs are recognized as robust modulators of the main senescence regulatory programs, the p53/p21 pathway, the pRB/p16 pathway, SASP, and protein patterns controlling these and other facets of senescence (Fig. 1, Tables 1-3). Various SA-ncRNAs described here (e.g., *UCA1*, *MEG3*, and *ANRIL*) can promote senescence by enhancing the production of growth-inhibitory, pro-senescence factors such as p53, p21, and p16. Other ncRNAs (e.g., let-7, miR-34, miR-519, and *lincRNA-p21*) can inhibit the synthesis of proliferative proteins, thereby enhancing senescence. Additional regulatory ncRNAs, such as miR-146a, miR-155, and miR-21, modulate SASP by controlling IRAK1 and TLR production, in turn influencing the secretory and inflammatory states. Other ncRNAs affecting mitochondrial function, telomere integrity, and chromatin metabolism have also been linked to senescence.

As we gain a deeper understanding of the expression and function of SA-ncRNAs, we can expect to find that many of these ncRNAs have clinical value in diagnosis and therapy. The ease of detection of ncRNAs in bodily fluids, particularly blood, make these RNAs particularly attractive as diagnostic and possibly also prognostic biomarkers. We anticipate that detecting SA-ncRNAs could be informative in conditions where senescence can predispose or exacerbate disease processes. Targeting ncRNAs may also be of therapeutic interest, whether the goal is to increase or suppress ncRNA levels for clinical benefit. The past few years have witnessed great progress in the development of technologies for delivering therapeutic RNA with increasing precision and efficacy. Advances in the design of viral vectors for RNA delivery, the development of cell-specific RNA aptamers, nanotechnology, and the widespread adoption of CRISPR (clustered regularly interspaced palindromic repeats)-Cas9-mediated interventions have greatly intensified our ability to repress and enhance gene expression with unprecedented accuracy. Similar to other highly specific therapeutic approaches, designing effective delivery systems that selectively target specific tissues remains an important roadblock for these promising treatment methods. With rapid progress in strategies to overcome these obstacles, interventions to modulate the

levels of beneficial and harmful ncRNAs affecting senescent processes will progressively become commonplace.

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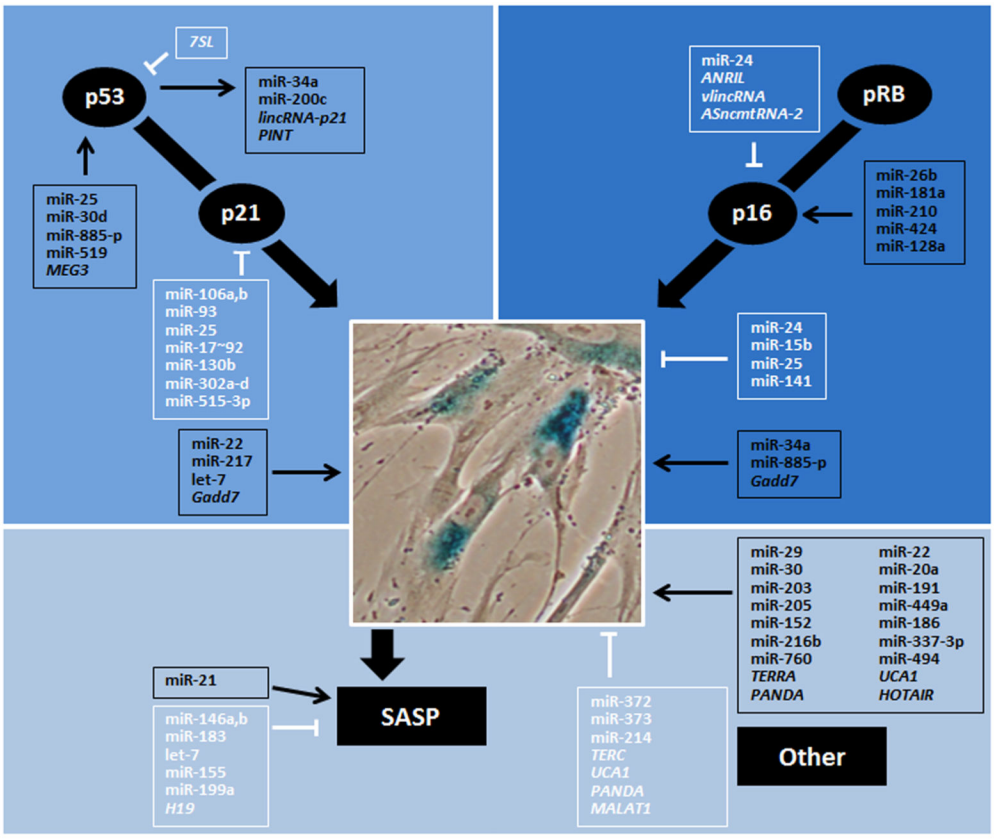

Figure 1. ncRNAs promoting and inhibiting senescence

Schematic representation of the main microRNAs and lncRNAs that promote (black) or inhibit (white) senescence phenotypes driven by p53/p21 (*top left*) pRB/p16 (*top right*), SASP and other mediators (*bottom*). *Center*, senescent fibroblasts displaying blue color indicative of SA-β-galactosidase (SA-β-gal) activity.

Table 1

ncRNAs involved in p53/p21-triggered senescence.

ncRNA	Senescence-associated Target	References
miR-34a	*E2F* mRNA	[72,73]
	BCL2 mRNA	[79]
	MYC mRNA	[79]
	SIRT1 mRNA	[74]
miR-22	*SIRT1* mRNA	[76]
miR-217	*SIRT1* mRNA	[77]
miR-138	*SIRT1* mRNA	[78]
miR-181a,b	*SIRT1* mRNA	[78]
let-7	*EZH2* mRNA	[84]
	HMGA2 mRNA	[83]
miR-200c	*ZEB1* mRNA	[86]
miR-25	*p53* mRNA	[87]
miR-30d	*p53* mRNA	[87]
miR-885-p	*MCM5* mRNA	[88]
	CDK2 mRNA	[88]
miR-519	*ORAI1* mRNA	[89,90]
	ATP2C1 mRNA	[89,90]
miR-106a,b	*p21* mRNA	[91,92]
miR-93	*p21* mRNA	[91]
miR-25	*p21* mRNA	[91]
miR-130b	*p21* mRNA	[93]
miR-302a,b,c,d	*p21* mRNA	[93]
miR-515-3p	*p21* mRNA	[93]
MEG3	MDM2	[95-98]
Gadd7	TDP-43	[100]
lincRNA-p21	*CTNNB* mRNA	[62]
	JUNB mRNA	[62]
PINT	PRC2	[105]
7SL	*p53* mRNA, SRP	[63]

Table 2

ncRNAs involved in pRB/p16-triggered senescence.

ncRNA	Senescence-Associated Target	References
miR-34a	*E2F* mRNA	[73]
miR-24	*p16* mRNA	[110,111]
miR-24	*MKK4* mRNA	[113]
miR-15b	*MKK4* mRNA	[113]
miR-25	*MKK4* mRNA	[113]
miR-141	*MKK4* mRNA	[113]
miR-26b	*CBX7*, *EED*, *EZH2*, *SUZ12* mRNAs	[112]
miR-210	(encoded PcG factors are repressed	[112]
miR-181a	jointly by the microRNAs)	[112]
miR-424		[112]
miR-128a	*BMI1* mRNA	[114]
Gadd7	TDP-43	[100]
ANRIL	CBX7	[116]
vlincRNA	H2A.Z	[121]
ASncmtRNA-2	(recursor of miR-4485, miR-1973)	[122]

Table 3

ncRNAs involved in SASP and additional senescence-associated events.

ncRNA	Senescence-Associated Target	References
Let-7	TLR7	[127]
miR-21	TLR7	[126]
miR-21	TLR8	[126]
miR-146a,b	*IRAK1* mRNA	[123]
miR-183	*ITGB1* mRNA	[125]
miR-155	*IKK* mRNA	[123]
miR-199a	*IKK* mRNA	[123]
TERC	TERT, telomerse	[133,135]
TERRA	Telomeres	[138-141]
MALAT1	B-MYB	[164]
HOTAIR	PRC2,Ub-proteasome	[169]