Minireview

Selenoproteins and the senescence-associated epitranscriptome

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Impact Statement

This article serves to shift current paradigms relating to our overall understanding of the control of senescence and to redefine the contribution of selenium, selenoproteins, and epitranscriptomic signals in senescence progression. Selenoproteins are important for the maintenance of normal organismal function, and we review their vital role in senescence programming. We identify epitranscriptomic defects key to selenocysteine utilization that also engage senescence and summarize the key role that selenoproteins have in degenerative disease progression. This serves to open an area of investigation linking defects in the epitranscriptome to senescence engagement. Thus, selenoproteins and epitranscriptomic writers may act as gatekeepers in controlling the senescent microenvironment through reactive oxygen species (ROS) mitigation and limiting the senescence-associated secretory phenotype. This review will serve as a compendium for those seeking to modulate epitranscriptomic systems as therapeutic avenues for treatment of age-related disease.

Abstract

Selenium is a naturally found trace element, which provides multiple benefits including antioxidant, anticancer, and antiaging, as well as boosting immunity. One unique feature of selenium is its incorporation as selenocysteine, a rare 21st amino acid, into selenoproteins. Twenty-five human selenoproteins have been discovered, and a majority of these serve as crucial antioxidant enzymes for redox homeostasis. Unlike other amino acids, incorporation of selenocysteine requires a distinctive UGA stop codon recoding mechanism. Although many studies correlating selenium, selenoproteins, aging, and senescence have been performed, it has not yet been explored if the upstream events regulating selenoprotein synthesis play a role in senescence-associated pathologies. The epitranscriptomic writer alkylation repair homolog 8 (ALKBH8) is critical for selenoprotein production, and its deficiency can significantly decrease levels of selenoproteins that are essential for reactive oxygen species (ROS) detoxification, and increase oxidative stress, one of the major drivers of cellular senescence. Here, we review the potential role of epitranscriptomic marks that govern selenocysteine utilization in regulating the senescence program.

Keywords: Senescence, SASP, selenium, selenoproteins, RNA modifications

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Biological theories of aging

In 2022, near 750 million people will reach the age of 65 years and above, and this population is expected to reach 1.6 billion by 2050. Increases in the elderly population will burden national health care systems at a great economic cost to society. Thus, it is important to better understand the underlying factors that drive aging and age-related disease. Aging is characterized by a gradual decline in systems' functions that result in progressive deterioration and loss of functionality at cellular, tissue, and organismal level.[1] A wide range of diseases – including neurodegenerative diseases, metabolic disorders, sensory changes, and cardiovascular diseases – have been shown to be associated with the aging process.[2,3] Understanding and identifying the regulators of age-associated functional decline are key to improving both the lifespan and health-span of individuals through the potential reversal of the aging hallmarks. Evolutionary theories attempt to explain the biological process of aging observed across many different species. Inspired from Charles Darwin's groundbreaking publication "On the Origin of Species" describing the evolution of natural selection, August Weismann proposed a "theory of programmed death," describing a specific death-mechanism designed by natural selection to eliminate

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the unfit, older generation to benefit the younger generation. He suggested that individual life span correlates with the limited number of cell divisions, which is determined at the embryonic stage. This idea was further developed as the theory of antagonistic pleiotropy theory, which explains that cell growth arrest is beneficial for organismal survival. In 1952, Peter Medawar proposed the theory of mutation accumulation, which posits that no known evolution mechanism exists to eliminate the mutations that cause deleterious effects on aged species.[4] This theory was later extended by George Williams' "Theory of antagonistic pleiotropy," explaining that although a pleiotropic gene can be beneficial for species survival early in life, that same gene can induce deleterious effects later in life.[5] For example, p53 prevents cancer development in young people by halting damaged cells from reproducing, but p53 can also play a role in aging as it impairs the ability to renew deteriorating tissues.[6] Thomas Kirkwood put forth the theory of "disposable soma" as an extension antagonistic pleiotropy theory, explaining that species need to balance the maintenance or repair of the cell or soma, and reproduction.[7] Mutations and cellular damage can accumulate over time as organisms focus their resources on reproductive maintenance because the body no longer has recourse to repair this damage. Genetic mutations that occur in egg or sperm cells will be passed onto future generations, whereas mutations occurring in other types of cells will only affect that individual cell and not be passed onto future generations. Most of these mutations are not fatal and are repaired and eliminated by repair mechanisms. The irreparable mutations will accumulate overtime, resulting in damage to cells and cell death. These mutations are the result of DNA damage that can be induced by oxygen containing free radicals, known as reactive oxygen species (ROS). Mitochondria are a major source of ROS and mutations in mitochondrial DNA can accumulate with age, resulting in further increases in ROS production and age-related functional decline.[8,9] In addition to DNA, ROS can also cause damage to proteins and lipids, commonly referred to as oxidative stress or oxidative damage, which contributes to many age-related diseases.[10]

Aging hallmarks and senescence

Cellular senescence is the biological process which limits the proliferation of cells in response to age-related damage. Cellular senescence was first described by L. Hayflick and P.S. Moorhead in 1961. Their observation showed that human cells in culture have a finite proliferative capacity, which describes "senescence" at the cellular level.[11] Cellular senescence, a process of irreversible cell cycle arrest, has proven to be a significant tumor restraining mechanism that terminates the proliferation of primary mammalian cells after limited number of population doublings, eliminating the potential detrimental effects of uncontrolled growth.[12–16] Cellular senescence can be induced by multiple factors, including telomere shortening, oxidative stress, and oncogene activation.[17–23] As cells senescence, they undergo a variety of biological changes creating a cellular microenvironment that is permissive to disease. Therefore, understanding the molecular triggers that control the senescent program will provide insight into limiting age-related disease onset.

Senescence stressors

Telomeres are specific DNA sequences composed of highly repetitive clusters of TTAGGG and the length is species-specific, varying from 4000 to 15,000 nucleotides. The length of telomeres shortens with each cellular replication due to the inability of DNA polymerase to work on single-stranded 3′ ends, which led to the "theory of marginotomy" by Olovnikov in 1972, which was experimentally confirmed by Blackburn.[24,25] Once telomeres reach critical threshold of shortening, the cells undergo cell cycle arrest, cellular senescence, and/or apoptosis.[21] Thus, the length of telomere serves as biological clock for cells' lifespan and a marker for cellular senescence. Whittemore *et al*.[26] demonstrated a correlation between telomere shortening rate and species-specific lifespan, indicating that those animals with slower telomere shortening rates display longer life span. Telomere shortening is accelerated when cells are exposed to cellular stressors, such as oxidative stress, resulting in reduced replicative capacity and premature senescence.[27–29] Scavenging ROS can slow down the rate of telomere shortening and extend the replicative capacity of a cells *in vitro*.[30,31]

Activation of DNA damage repair (DDR) and corresponding DNA repair pathways is a primary response to double-strand DNA breaks (DSBs), as well as telomere attrition due to persistent DNA damage, and can trigger activation of p53. The tumor suppressor gene, p53, plays a key role as a transcription factor in cell-cycle control, apoptosis, and cellular stress responses. p53 is highly unstable and is degraded through ubiquitin-mediated degradation by MDM2 in the absence of DNA damage.[32] DDR can block the progression of the cell cycle via stabilization of p53 through ATM or ATR kinases, leading to transcriptional activation of the cyclin-dependent kinase (CDK) inhibitor p21.[28] p53 has been recognized as a key modulator of cellular senescence, aging, and tumor progression.[33–35]

Oncogene-induced premature senescence is triggered in response to activation of oncogenes or to the loss of tumor suppressors genes.[18,36–39] Senescence can also be induced by cellular stresses, such as radiation, drugs, and oxidative stress, which is termed stress-induced senescence and can result in increased expression of the tumor suppressor and cyclin-dependent inhibitor $p16^{INK4a}$.[40–43]

The free radical theory of aging posits that accumulation of macromolecular damage occurs after a lifetime of exposure to oxidants.[20] Although often refuted, several tenets of this theory stand true including the two critical tenets focusing on species-specific low mitochondrial ROS generation rates at Complex I of the electron transport chain (ETC) and lowered levels of fatty acid unsaturation on cellular and mitochondrial membranes in long-lived animals.[44] The mechanistic control of senescence by ROS has also garnered significant focus.[45] Figure 1 summarizes the many cellular stresses discussed above that can induce senescence.

Mitochondria and cellular senescence

Mitochondria, cellular powerhouses that generate energy from fuel, are crucial for cellular bioenergetics, and play major role in calcium signaling, redox homeostasis, and thermogenesis. Mitochondria also serve as a major source

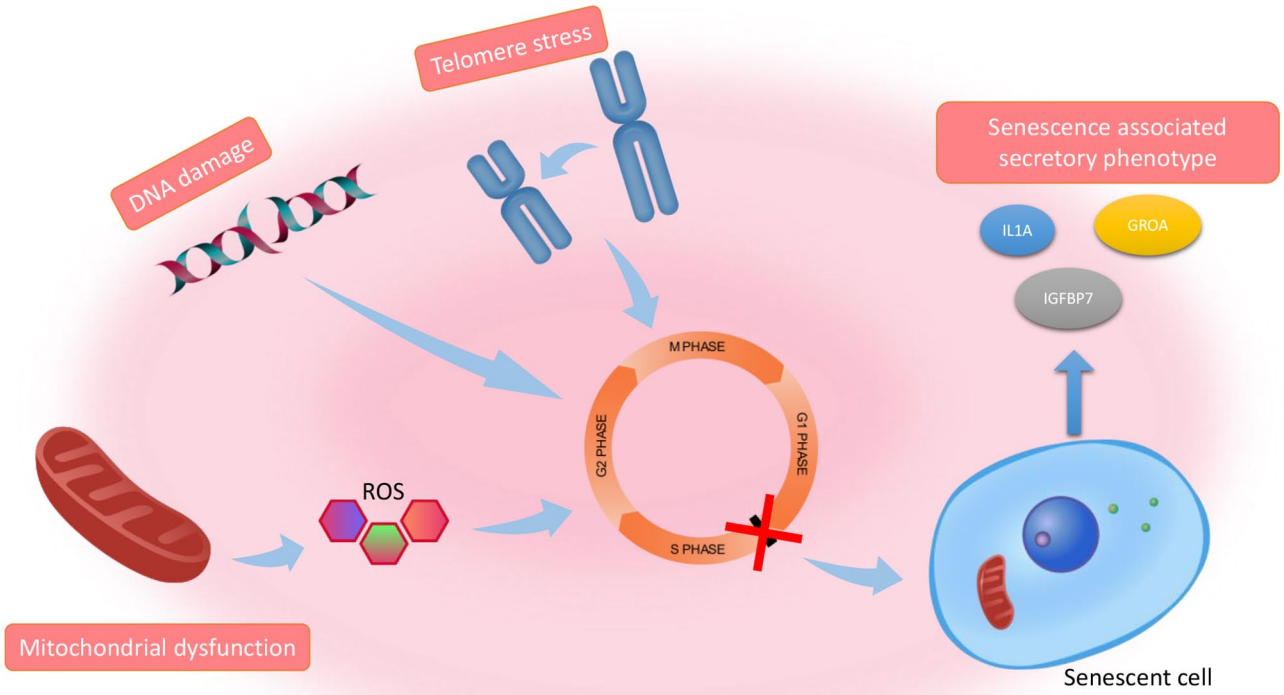

Figure 1. Common senescence-inducing stressors (see the text for details). (A color version of this figure is available in the online journal.)

of ROS production, which are generated during oxidative phosphorylation (OXPHOS) primarily as a result of electron leak and the $1-e^-$ reduction of molecular oxygen (O_2) to superoxide ($O_2^{\bullet-}$).[46] OXPHOS utilizes five protein complexes, ubiquinone oxidoreductase (Complex I), succinate dehydrogenase (Complex II), ubiquinol-cytochrome c oxidoreductase (Complex III), cytochrome c oxidase (Complex IV) and adenosine triphosphate (ATP) synthase (Complex V), to provide chemical energy for cell survival.[47] Most of the subunits of Complexes I, III, IV, and V are synthesized on cytosolic ribosomes, followed by transport and assembly into the mitochondrial membrane, and 13 subunits of these complexes are synthesized by mitoribosome and rapidly inserted into the mitochondrial inner membrane.[48] During OXPHOS, ATP synthesis is achieved by generating proton motive force through series of electron transfer processes, in which the electron donors, nicotinamide adenine dinucleotide (NADH) and succinate, are oxidized by Complexes I and II, respectively, followed by transfer of electrons to Complex IV through Complex III, where the electrons are reduced to molecular oxygen.[48] The concentration of potential electron donors and the production rate of ATP can influence the flux of $O_2^{\bullet-}$[49] that is generated from Complexes I and II in the mitochondrial matrix, and in both the matrix and intermembrane space by Complex III.[50,51] $O_2^{\bullet-}$ generated from Complex III can travel into the cytosol for signaling purposes[52] or be enzymatically dismuted to H_2O_2 by superoxide dismutase proteins, SOD1 and SOD2.[53,54] Deterioration in mitochondrial OXPHOS is primarily involved in early stages of cellular senescence, and increased ROS production from dysfunctional mitochondria can aggravate senescence by enhancing DNA damage and the DDR.[55–62]

During the coupled processes of electron transport and OXPHOS, an electrochemical gradient is created between the mitochondrial matrix and intermembrane space. The protons from the intermembrane space are transported into the matrix by ATP synthase, driving the conversion of adenosine diphosphate (ADP) into ATP. In addition to ATP synthase, protons can also leak into the matrix by action of specialized mitochondrial carriers termed uncoupling proteins (UCPs), generating heat at the expense of ATP production in a process termed thermogenesis.[63] UCPs are located at the inner membrane and are involved in redox regulation and metabolic processes.[64] Thermogenesis mainly occurs in brown adipose tissue (BAT) through uncoupling protein 1 (UCP1).[65,66] Unlike UCP1, which is mainly expressed in BAT, UCP2 and UCP3 are expressed in multiple tissues and their uncoupling activities have been linked to the pathogenesis of age-related metabolic disorders and cancers, rather than thermogenesis.[67–72] Overexpression of UCP2 in macrophages can reduce ROS production and downregulation of UCP2 can increase ROS production, indicating a role for UCP2 in modulating ROS production.[73,74] Although studies correlating dysfunction of UCPs to age-related metabolic disorders exist, further research is necessary to determine if UCPs are potential targets for age-related molecular management.

Maintenance of mitochondrial dynamics is key to controlling mitochondrial homeostasis, and involves fusion, fission, and mitophagy.[75,76] Fusion and fission events serve to control mitochondrial quality. During cell cycle progression,

mitochondria elongate in the G1/S phase to increase the ATP supply, which is necessary for cell duplication, and fragment in the G2/M phase to partition damaged material to daughter organelles, as well as to be equally divided to daughter cells.[77–80] In mammalian cells, large dynamin-related GTPases termed mitofusin 1 (MFN1), mitofusin 2 (MFN2), and optic atrophy protein 1 (OPA1) primarily orchestrate mitochondrial fusion.[81,82] MFN1 and MFN2 are outer mitochondrial membrane (OMM) proteins and mediate the first step of mitochondrial fusion by dimerization of MFN1-MFN2 or MFN2-MFN2, whereas OPA1 is situated within the intermembrane space and mediates fusion of the inner mitochondrial membrane (IMM). The main players of mitochondrial fission are dynamin-related protein 1 (DRP1) and mitochondrial fission 1 protein (FIS1).[83] Highly elongated mitochondria and increased mitochondrial content are observed in stress-induced premature senescence.[59] Lee *et al.*[84] demonstrated that mitochondrial elongation is associated with an increased ratio of fusion to fission proteins (MFN > DRP1 and/or MFN > FIS1). Blocking mitochondrial fission induces mitochondrial elongation engages the senescence phenotype and increases ROS production, while overexpression of FIS1 protein blocks mitochondrial elongation and partially reverses the senescence phenotype. These findings indicate that fusion/fission imbalance can trigger senescence-associated changes.[84,85]

Senescence-associated secretory phenotype

Upon senescent transformation, senescent cells maintain metabolic activity and undergo distinct secretome alterations. Termed the senescence-associated secretory phenotype (SASP), the SASP involves the secretion of soluble factors, such as interleukins, chemokines, and growth factors, as well as degradative matrix metalloproteases (MMPs) and insoluble extracellular matrix (ECMO) components which can alter the tissue microenvironment and affect cellular behavior.[86,87] Cellular senescence acts as a tumor constraining mechanism by guarding against the unrestricted growth of damaged cells.[88] Senescence has also been shown to participate in embryonic development, tissue repair and wound healing.[89–93] While senescence is beneficial as an innate tumor-suppressive mechanism responsible for inducing permanent replicative arrest in cells at risk of malignant transformation, the accumulation of senescent cells with increasing age is deleterious in tissue microenvironments *in vivo*.[94] Through its ability to evoke responses from cells in a paracrine fashion, SASP has been linked to numerous age-associated disease pathologies including tumor invasion, cardiovascular dysfunction, neuroinflammation, osteoarthritis, and renal disease.[86,95–97]

Selenium and cellular senescence

Selenium was first discovered by the Swedish chemist Jons Jakob Berzelius, in 1817 while its potential health benefits were not realized until 1957, when Klaus Schwartz and Clavin Foltz determined that dietary selenium protected rats against liver necrosis.[98] It is now well established that selenium is essential for several aspects of human health, including central nervous system, endocrine, cardiovascular, muscle, and immune function.[99,100] Many studies have revealed correlations between selenium deficiencies and increased risks of developing many pathologies, including cancer, neurodegenerative diseases, cardiovascular disorders, and infectious diseases.[99–103] Selenomethionine is the predominant form of selenium ingested by humans and dietary selenium can be obtained through a wide variety of foods, including grains, vegetables, seafood, meat, and dairy products.[104] Selenium is metabolized into various small molecular weight seleno compounds that can affect cellular processes such as DNA repair and epigenetics.[105,106] Strong interplay between selenium, selenoproteins and replicative senescence has been demonstrated by a proteomic study that showed a 72% overlap between proteins induced by senescence and those by selenium deprivation.[107] Selenium supplementation in cell culture medium can delay the onset of replicative senescence and prolong selenoprotein expression, while selenium depletion slows cell proliferation.[108] The Nove Italy study demonstrated that serum selenium and selenium-dependent glutathione peroxidase (GPx) activity decreases with age, especially in people over 60 years of age[109] with similar observations reported by Lahcene and coworkers in Western Africa.[110] An increasing number of studies have shown that selenium's antioxidant activity is essential in combating aging and a weakened antioxidant capacity promotes senescence, aging, and age-related disease.[111]

Selenoproteins

A unique feature of selenium is that it is incorporated as selenocysteine (Sec) into 25 and 24 human and rodent selenoproteins, respectively. Selenocysteine offers a distinct advantage over cysteine alone as it can participate in reactions that are readily reversed with equilibrium constants of an order of magnitude higher than similar reactions involving sulfur. Sec is also used in enzymes because it resists inactivation by oxidation. We refer the reader to a review by Maroney and Mondal on the many beneficial chemical attributes of Sec.[112] Many selenoproteins play a role in maintaining redox homeostasis, serving as antioxidant enzymes to protect against oxidative stress. Selenoproteins are key regulators of stress responses, metabolism, and immunity, and can be classified into six functional groups: peroxidase/reductase activity, redox signaling, hormone metabolism, protein folding, selenium transport, and Sec synthesis.[113,114] Examples include selenoprotein K, S, H, N, GPx1–4, and TrxR1–3. Selenoprotein V, W, and GPx4 play vital roles in embryonic vitality and development. Selenophosphate synthase, selenoprotein P (SEPP), and selenoprotein 15 (SEL 15) are involved in the synthesis and transportation of selenium. Recent work indicates that selenophosphate synthetase 1 (SEPHS1) loss is associated with chondrocyte senescence in both human and murine osteoarthritis.[115] The deiodinase family (DIO1–3) of selenoproteins regulates thyroid hormone and thyroid function (see the comprehensive review by Leonardi *et al.*[116] for detail). As redox signaling is essential in regulating many characteristics of cancer cells and selenoproteins maintain

redox homeostasis, selenoprotein links to cancer are extensively reviewed as well.[117–120] Among 25 human selenoproteins, GPx1 is one of the best-characterized selenoproteins, and can reduce H_2O_2 and lipid hydroperoxidases utilizing glutathione as an electron donor. GPx1 is expressed in almost all cell types and is critical to maintaining proper redox balance under stress, as GPx1[121]-deficient mice are susceptible to ROS-inducting agents such as H_2O_2 and lung inflammation and damage due to influenza infection and cigarette smoke.[122–124] Thioredoxin is maintained in its reduced and active state by thioredoxin reductase (TrxR) and reduces disulfide bonds, which is required for maintaining a reducing environment.[137] Knockout of both TrxR1 and TrxR2 in mice results in severe growth abnormality and embryonic death, demonstrating TrxRs are also important for development.[125–127] Table 1 provides a comprehensive assessment of all known selenoproteins and their age-related disease relevance.

Table 1. Selenoproteins and senescence.

Identity	Name	Function	Putative role in cellular senescence or aging	Functional group
Glutathione peroxidase 1	GPx1	Reduces H_2O_2 and lipid hydroperoxidases.[165]	GPx1 transgenics display protection from renal aging.[166]	Antioxidative capacity Peroxidase/reductase activity
Glutathione peroxidase 2	GPx2	Expressed primarily in gastrointestinal tract, where it reduces both inorganic and organic peroxides.[167]	Implicated in the modulation of cell fate decisions and the maintenance of mucosal homeostasis.[167]	
Glutathione peroxidase 3	GPx3	Acts as an antioxidant defense enzyme.[168]	Age-related decreases are associated with increased risk of cardiovascular events.[169]	
Glutathione peroxidase 4	GPx4	Thought to counteract mitochondrial lipid peroxidation in mammals.[165]	Implicates in neurodegeneration due to its role in limiting ferroptosis.[170]	
Glutathione peroxidase 6	GPx6	Expression has been documented in embryos and olfactory epithelium.[171]	Shortens lifespan of *Caenorhabditis elegans* when mutant in combination with GPx-1, 2, and 7.[172]	
Selenoprotein K	SEL K	Localized in the endoplasmic reticulum, where it is implicated in ER-associated degradation of misfolded proteins.[173]	Thought to contribute to the protection of cells from ER stress–induced apoptosis. Studies in mice demonstrated its importance in promoting Ca(2+) flux in immune cells and mounting effective immune response.[173]	
Selenoprotein R (methionine sulforeductase B)	SEL R	Catalyzes the reduction of methionine-R-sulfoxides to methionine, thereby protecting cells from oxidative stress and protein repair.[174]	Downregulated during replicative senescence.[175]	
Selenoprotein W	SEL W	Thioredoxin-like function.[176]	Regulated osteoclast differentiation and blocks osteoporosis.[177]	
Iodothyronine deiodinase 1	DIO1	Regulates thyroid hormone.[178]	Plays an essential role in modulating thyroid function.[178]	Thyroid hormone metabolism
Iodothyronine deiodinase 2	DIO2	High expression in brain and thyroid, where it catalyzes the conversion of pro-hormone thyroxine to the bioactive thyroid hormone.[179]	Crucial in the regulation of thyroid hormone action and correlated with increases in thyroidal T3 production.[180]	
Iodothyronine deiodinase 3	DIO3	Shown to catalyze the inactivation of thyroid hormone to inactive metabolites through inner-ring deiodination of thyroxine and triiodothyronine hormones.[178]	Strong potential to limit influence tissue dysfunction in human thyroid disorders.[181]	
Thioredoxin reductase 1	TrxR1	Involved in the reduction of thioredoxins and other substrates.[182]	Critical in the regulation of the redox metabolism. Mounting studies suggest that TrxR1 inhibits multiple stages of tumor progression including protection against malignant transformation.[182]	Redox signaling
Thioredoxin reductase 2	TrxR2	Mitochondrial thioredoxin-disulfide reductase activity.[183]	Increased expression is associated with enhanced longevity.[184,185]	
Thioredoxin reductase 3	TrxR3	Implicated in redox regulation in bacteria.[182]	Associated with amyloidosis.[182]	
15kDA selenoprotein	SEL15	Involved in the quality control of glycoprotein folding.[186]	Crucial function in glycoprotein folding and redox homeostasis; SEL15-deficient cells demonstrated improper folding of lens proteins.[186]	Protein folding
Selenoprotein M	SEL M	Exact function unknown, linked to onset of neurodegenerative diseases.[187]	Associated with the maintenance of oocyte maturation.[188]	
Selenoprotein N	SEL N	Localized in the endoplasmic reticulum as calcium sensor.[189]	Protects cells again oxidative stress through its involvement in redox-related calcium homeostasis. Some mutations are linked to the premature development of muscle disorders.[189]	
Selenoprotein S	SEL S	Expressed in the endoplasmic reticulum, where it modulates the protein folding process.[190]	Plays a role in regulating lipid accumulation and insulin actiong.[191]	

(Continued)

Table 1. (Continued)

Identity	Name	Function	Putative role in cellular senescence or aging	Functional group
Selenophosphate synthetase 2	SPS2	Functions as a selenium donor during mammalian selenocysteine synthesis.[192]	Deficiency exacerbates osteoarthritis.[115]	Selenium synthesis
Selenoprotein P	SEL P	Acts as an extracellular antioxidant and transports selenium to extra-hepatic tissues via apolipoprotein E receptor-2 (apoER2).[193]	Required for exercise-induced adult hippocampal neurogenesis.[194]	Selenium transport and storage
Selenoprotein H	SEL H	Demonstrates oxidoreductive activity. Implicated in the inhibition of apoptotic cell death pathways and neuron protection against UVB-induced damage.[195]	Involved in the suppression of cellular senescence through redox and genome regulation. Promotes mitochondrial function and biogenesis.[195]	No functional group assigned.
Selenoprotein I	SEL I	Crucial to the production of phosphatidylethanolamine by catalyzing the synthesis of phosphoethanolamine from CDP-ethanolamine to diacylglycerol.[196]	Essential for murine embryognesis.[197]	
Selenoprotein O	SEL O	Shown to participate in bacterial protein ampylation.[198]	Implicated in maintenance of mitochondrial function in response to selenomethionine supplementation in murine AD models.[199]	
Selenoprotein T	SEL T	Thioredoxin-like structure with oxidoreductase activity.[200]	Protects dopaminergic neurons against oxidative stress and premature cell death.[201]	
Selenoprotein V	SEL V	Primary expression in testis with thioredoxin-like fold and potential redox function.[202]	Confers protection against reactive oxygen and nitrogen species.[203]	

ER: endoplasmic reticulum; UVB: ultraviolet B; AD: Alzheimer's disease.

Stop codon recoding and alkylation repair homolog 8

Production of the selenoproteins requires incorporation of a rare 21st amino acid, Sec via specialized translation known as UGA stop codon recoding. Epitranscriptomic marks on $tRNA^{Sec}$ – along with the elongation factor (EFSec), selenocysteine insertion sequence (SECIS) in 3′ UTR, and SECIS-binding protein 2 (SBP2) – are essential for selenoprotein synthesis. The epitranscriptomic marks are tRNA modifications found on the anticodon wobble uridine (U), which are catalyzed by multiple enzymes. The U is carboxymethylated to methyluridine (cm^5U) by elongator protein complex (ELP),[128,129] with cm^5U then methylated to 5-methoxycarbonylmethylluridine (mcm^5U) in $tRNA^{Sec}$ by the tRNA methyltransferase alkylation repair homolog 8 (ALKBH8)[130,131] (Figure 2). The nine ALKB homologs, ALKBH1–8 and the fat mass obesity–associated protein (FTO), are some of the most well-characterized 2-oxoglutarate and Fe(II)-dependent dioxygenase superfamily members. Mammalian alkylation repair homolog 8 (ALKBH8) is the only ALKBH protein family with both a RNA binding motif and multifunctional methyltransferase domain and methyltransferase subunit, Trm112m, that functions as an epitranscritomic writer, which has been linked to wobble-uridine modifications.[121,162] In an ALKBH8 and selenium-dependent manner, another isoform of $tRNA^{Sec}$ is created by adding 2′-O-ribose methylation to make 5-methoxycarbonylmethyl-2′-O-methyluridine (mcm^5Um) using mcm^5U as precursor.[131–135] While the mcm^5U isoform serves in the synthesis of housekeeping selenoproteins, the mcm^5Um isoform is sensitive to selenium and ROS status and is involved in the translation of stress response selenoproteins.[133–137] The wobble-uridine modifications mcm^5U and mcm^5s^2U are also found on $tRNA^{Arg\ and\ Gly}$ and $tRNA^{Lys,\ Glu,\ and\ Gln}$, respectively.

While ALKBH8 is linked to the modification of six different tRNAs, defects have largely been attributed to hypo-modified $tRNA^{sec}$ leading to decreased selenoprotein synthesis and corrupted ROS detoxification.[135] ALKBH8 deficiency leads to increased ROS and DNA damage and sensitizes tissues to toxicants that promote stress.[135,138–140] Defects in ALKBH8 in humans have been linked to developmental disorders and intellectual disability, with overexpression linked to cancer proliferation.[141,142] Decreased expression of selenoproteins was observed in transgenic mice encoding an AUG mutation in the $tRNA^{Sec}$ gene at position 37.[143] Overexpression of the G37 $tRNA^{Sec}$ mutant led to changes in the distribution of the mcm^5U and mcm^5Um modifications and dysregulated-specific stress responsive selenoproteins, revealing that selenoproteins responsive to selenium status are involved in stress-related functions.[137,144]

Epitranscriptomic writer defects engage senescence

Mouse ALKBH8 deficiency promotes increased ROS and SASP markers[140] and similarly sensitizes HEK293 cells to the agents that promote ROS.[145] It has been established that cellular senescence increases steady-state H_2O_2 and that limiting senescence-associated increases in H_2O_2 extend cellular lifespan.[146] The majority of mitochondrial H_2O_2 consuming activity is largely reliant on the activities of the Sec containing mitochondrial TrxR and GPx enzymes.[147] Loss of ALKBH8 in mouse embryonic fibroblasts induced wobble-uridine modification of $tRNA^{sec}$, as well as $tRNA^{Glu(UUC)}$ and $tRNA^{Arg(UCU)}$, and disrupted recoding of the UGA stop codon to Sec, resulting in increased cellular oxidizing capacity and reduced synthesis of GPx and TrxR1 selenoenzymes.[121,162] This impairment in Sec utilization[140] arising from ALKBH8 deficiency induces cellular senescence,

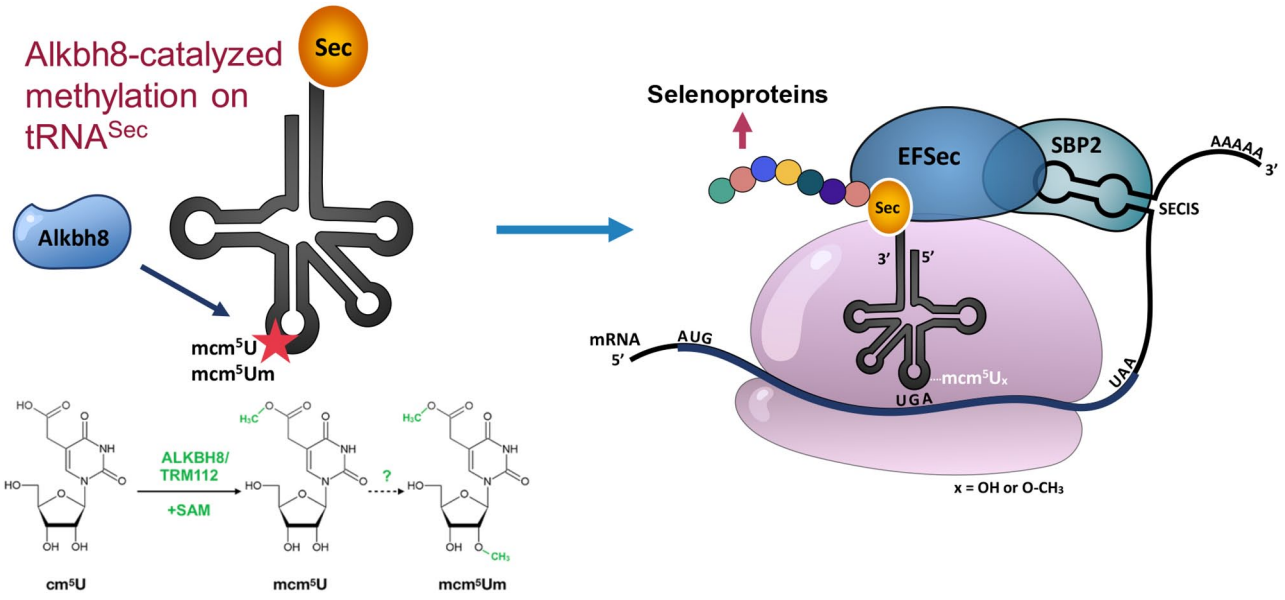

Figure 2. Schematic of selenoprotein synthesis (see the text for details). (A color version of this figure is available in the online journal.)

providing an exciting link between the epitranscriptomic signals mcm^{5}U and mcm^{5}Um, the efficiency of UGA recoding and senescence.[135,140]

Cellular senescence is accompanied by growth arrest, and ALKBH8-deficient MEFs display a significant proliferative defect and modulate many facets of the senescent program including increases in levels of p16^{Ink4a}, heterochromatic foci, senescence-associated β-Gal, mitochondrial fusion, and many prominent SASP transcripts.[140] The SASP is characterized by high levels of inflammatory cytokines, including interleukin (IL)-6 and IL-8, and studies have shown that they are under redox control.[148,149] Limiting oxidant detoxification by restricting Sec utilization in ALKBH8-deficient MEFs impacts SASP levels,[140] and a similar response is observed in renal tissue from 24-month-old ALKBH8-deficient mice Figure 3.

A number of studies have demonstrated that senescence, in distinct cellular systems, is accompanied by increases in basal oxygen consumption rate (OCR).[150,151] We have demonstrated that the ALKBH8 deficiency is accompanied by a robust increase in basal OCR and glycolytic activity that is associated with increased expression of the uncoupling protein UCP2.[140] UCP2 is ubiquitously expressed in most cell types and is thought to limit mitochondrial superoxide production by relieving any impedance in electron flux through the respiratory chain.[152] Stanniocalcin 1 (STC-1) is a homodimeric glycoprotein that is expressed in a wide variety of tissues with autocrine or paracrine functions and identified as one of four SASP factors that is commonly induced by distinct senescence activators.[153] STC-1 has been implicated, as endogen with neuroprotective function with the ability to limit superoxide generation by inducing UCP in the mitochondria.[154–156] It is exciting to speculate that selenoprotein loss resulting from ALBH8 deficiency induces senescence-associated STC-1 to drive UCP2 expression to restrict mitochondrial ROS production as detailed in Figure 4. Overall, these observations indicate that the levels of many of the

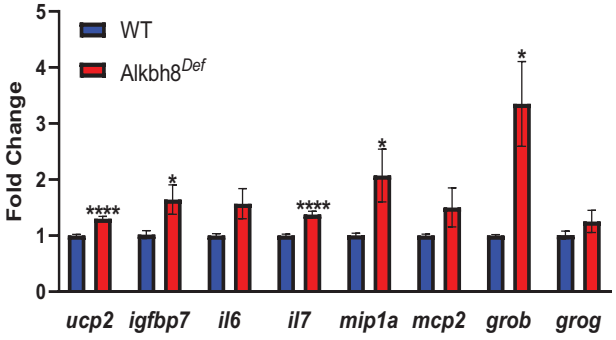

Figure 3. Global selenocysteine deficiency in 24-month-old selenoprotein-deficient mice exacerbates SASP *in vivo*. RT-PCR from kidneys of WT and Alkbh8^{Def} mice.[139] Data are presented as mean ± SEM, $n = 3$. Unpaired Student's *t*-test is used for statistical analysis. RT-PCR and primers utilized as described by Lee *et al.*[140] (A color version of this figure is available in the online journal.) $^*P < 0.05$; $^{****}P < 0.0001$.

most prominent SASP markers are dramatically upregulated when Sec utilization is impaired by ALKBH8 deficiency both *in vitro* and *in vivo*.

During RNA maturation, over 170 different enzyme-catalyzed modifications can be made to RNA molecules, and the nature and quantity of these modifications can differ drastically between species, cells, and organelles. Most of these modifications occur in ribosomal and transfer RNAs, but they also appear in small nucleolar RNAs, small nuclear RNAs, microRNAs, small interfering, and Piwi-interacting RNA.[157] RNA modifications can influence the maturation, structure, function, and degradation of modified RNAs, and have a major influence on gene expression. RNA modifications play crucial regulatory roles in many cellular processes, including stem cell differentiation and self-renewal,[158] neural function and development,[159] and responses to toxins and environmental stresses.[160] These modifications also play important roles in regulating various hallmarks of aging. *TFB1M*, a gene for a methyltransferase that modifies the

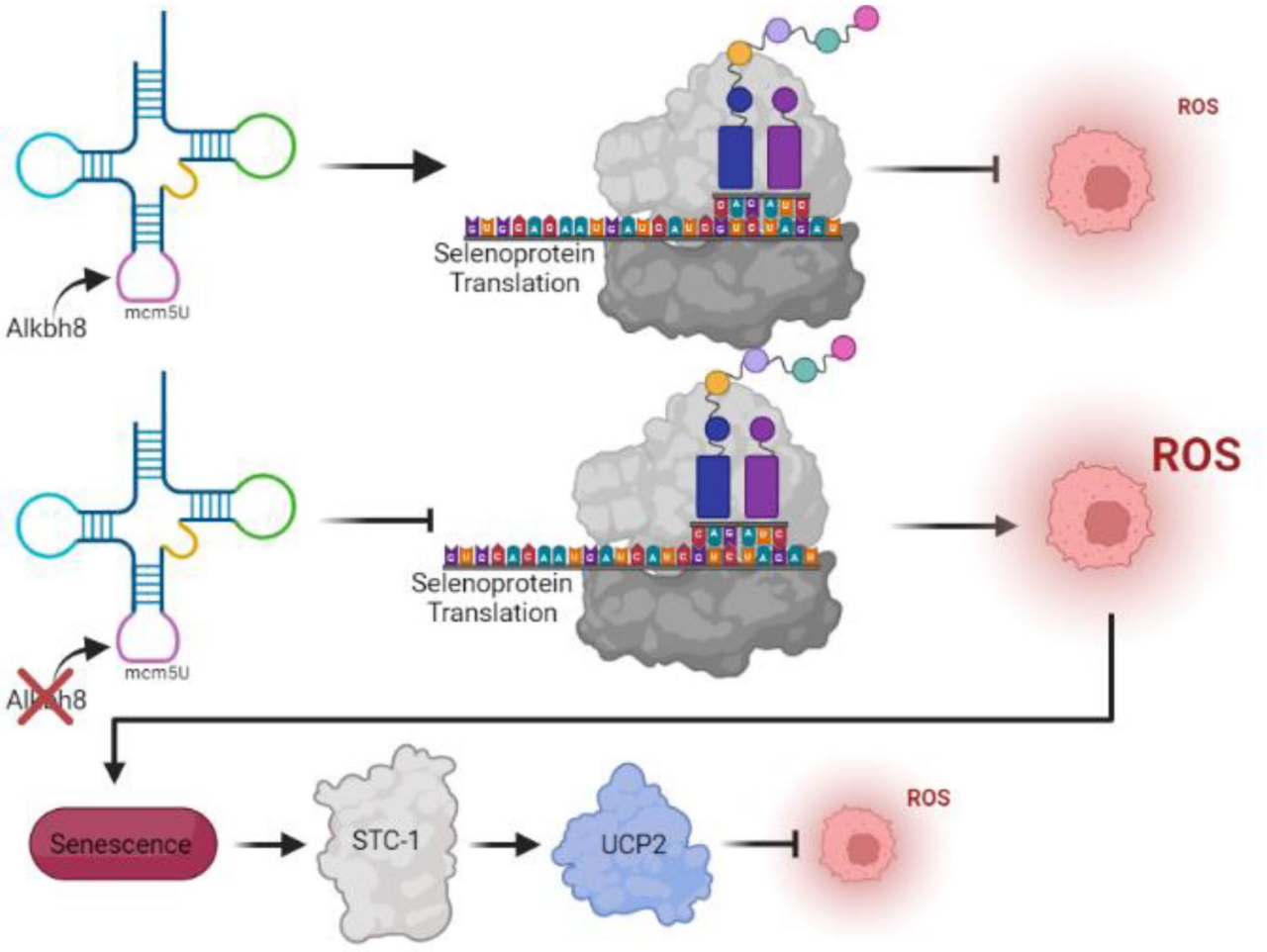

Figure 4. Role of senescence-associated STC-1 in limiting mitochondrial ROS production in response to selenoprotein deficiency. UCP-2 induction in response to selenoprotein loss resulting from ALKBH8 deficiency is potentially regulated by the SASP factor stanniocalcin-1 and serves to restrict mitochondrial ROS production. (A color version of this figure is available in the online journal.)

mitochondrial 12S rRNA, is essential for the 12S rRNA's stability,[161] and TFB1M$^{+/-}$ mice have impaired mitochondrial translation in pancreatic islet cells and an impaired insulin response.[162] Genetic analyses in humans have shown *TFB1M* to be a risk gene for type 2 diabetes.[163] In the context of stem cell exhaustion, depletion of the m^{6}A reader YTHDF2 significantly increased the quantity of hematopoietic stem cells in mice, while knocking down the *YTHDF2* gene in *ex vivo* human hematopoietic stem cells led to a fivefold increase in their quantity, demonstrating YTHDF2's importance to stem cell maintenance.[164] Overall, these studies suggest that epitranscriptomic defects are linked to human disease and senescence onset and modulation of specific RNA writers, readers, and erasers may lead to therapeutic interventions to selectively modulate the senescence program.

Summary

Here, we connect selenium and the epitranscriptomic control of Sec utilization by ALKBH8 to the regulation of senescence. Selenium deficiency has been linked to many age-related disease pathologies; it is also highly likely that conditions that disrupt Sec utilization or interfere with ALKBH8 function drive senescence. This review fills a basic scientific knowledge gap specific to the contribution of epitranscriptomic writers and marks in regulating senescence. We address how cellular stress-responses are controlled, in part, by dynamic enzyme catalyzed tRNA modifications, classified as epitranscriptomic marks, that regulate translation and mitigate ROS production.[135] This article also provides insight into the role of epitranscriptomic marks in aging and disease, and similar to epigenetic marks, RNA modifications are attractive targets for new senescence-modifying therapeutics.

AUTHORS' CONTRIBUTIONS

All authors participated in the design, interpretation of the studies and analysis of the data, and review of the manuscript: MYL, SOB, DE, AS, TJB, and JAM. MYL, TJB, and JAM wrote the manuscript.

DECLARATION OF CONFLICTING INTERESTS

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