Chapter 10
Mitochondrial Reactive Oxygen Species in Cellular Senescence

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Abstract Mitochondria are central for the maintenance of cellular homeostasis and both cellular dysfunction and aging are linked to mitochondrial dysfunction. Mitochondrial dysfunction is the principle cause of increased levels of reactive oxygen species (ROS) and oxidative stress, which is a key mediator of aging. The cell responds to this stressful stimulus by the induction of the cellular aging-stress response, cellular senescence. Here, we discuss the mechanisms through which mitochondrial ROS promotes senescence. In this context, we will highlight how mitochondrial ROS serves an initiating upstream, or sustaining downstream, role in the induction of senescence. We will also discuss potential interventions to alleviate mitochondrial ROS and delay cellular senescence.

Keywords Aging • Cellular senescence • Mitochondria • ROS

10.1 Introduction: Mitochondria and Cellular Senescence

Mitochondria are essential for normal cellular processes including aerobic metabolism for the production of ATP and critical metabolic intermediates, calcium homeostasis, apoptotic signaling, beta oxidation, and regulations of redox status. Because mitochondria are central to energy metabolism and affect signaling pathways, they also play an important regulatory role in the cell. Specifically, mitochondria respond to cellular signals or altered status by communicating to the nucleus to alter gene expression through retrograde signaling. This is vital not only for adapting cellular energy status, but also for maintaining mitochondrial quality control. Mitochondrial defects are an acknowledged feature of cellular dysfunction in the aging process where the most prominent aspects of mitochondrial dysfunction include reduced function, structural disorganization, and increased production of reactive oxygen species (ROS). These alterations are common in aged tissues

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and are associated with age-related pathologies, yet the mechanisms by which mitochondrial dysfunction promotes cellular aging and tissue deterioration are unclear (Bratic and Larsson 2013; Lee and Wei 2012; Cagin and Enriquez 2015). One possibility is that mitochondrial dysfunction promotes the cellular aging-stress response, cellular senescence. Although senescent cells are metabolically active and viable (Campisi 2013), they exhibit alterations in mitochondrial morphology, function, metabolism, and redox state (Passos et al. 2013; Hutter et al. 2004; Hwang et al. 2009; Ahmed et al. 2010).

Since mitochondria are central to cellular metabolism, it is compelling to speculate the requirement of mitochondrial alterations in senescence. A major detrimental aspect of mitochondria dysfunction is the generation of ROS, which not only leads to cellular damage but also reinforces mitochondrial dysfunction by damaging mitochondrial components, altering mitochondrial metabolism and dynamics, and depleting antioxidant defenses (Bratic and Larsson 2013; Seo et al. 2010). As a result of amplified mitochondrial dysfunction, this stressed cellular state might then signal to promote senescence. In this review, we will focus on how mitochondrial ROS might serve as an effector of cellular senescence. We will also discuss potential therapeutic approaches to improve mitochondrial homeostasis and prevent the pathologic generation of ROS.

10.2 The Generation of Mitochondrial ROS

One of the first theories of aging proposed that free radical-generated ROS insidiously impaired cellular homeostasis and caused aging (Harman 1956). However, demonstration that antioxidants failed to slow the aging process in mammals led to revision of this theory, with mitochondria identified as being the principal endogenous source and target of ROS responsible for cellular aging (Harman 1972). Mitochondria produce ROS as a byproduct of oxidative phosphorylation when electrons, leaked mainly from complexes I and III of the electron transport chain (ETC), reduce oxygen into toxic superoxide anion. The ETC establishes a membrane potential across the inner mitochondrial membrane to control oxidative phosphorylation. Alteration of this membrane potential through hyperpolarization or depolarization accelerates the formation of superoxide anion (Korshunov et al. 1997; Nicholls 2004; Suski et al. 2012; Zorov et al. 2006). ETC-generated superoxide anion can be converted through redox reactions into intermediates and other harmful ROS, such as hydrogen peroxide, peroxynitrite anion, and hydroxyl radical (Turrens 2003; Brand 2010). The mitochondria maintain ROS levels and redox status using an endogenous antioxidant defense system consisting of the enzymes manganese superoxide dismutase (MnSOD), glutathione peroxidase, and thioredoxin 2 (Li et al. 2013b). High levels of ROS damage macromolecules, including mitochondrial DNA (mtDNA), proteins, and lipids; developing a model of vicious cycle where ROS produced in the mitochondria propagates further damage within the cell. The

mitochondrial genome is susceptible to ROS-induced mutagenesis because of its close proximity to ROS, absence of protective histones, and lower fidelity DNA repair system. ROS-induced mutagenesis compromises oxidative phosphorylation by incorporation of defective mtDNA-encoded subunits or altering complex stoichiometry within the ETC. mtDNA encodes 24 mitochondrial translation-related RNAs and 13 proteins that comprise subunits of the ETC complexes and ATP synthase. Also vulnerable to ROS is the tricarboxylic acid (TCA) cycle enzyme aconitase, which attempts to compensate for the production of ROS by slowing TCA cycle and ETC activity. However, slowing TCA cycle activity may not counteract, but worsen the production of ROS by malfunctioning ETC complexes (Bandy and Davison 1990; Shokolenko et al. 2014; Alexeyev 2009). The aforementioned actions form a feed-forward progression of ROS-damaged mitochondria, amplifying the production of ROS and damaging neighboring mitochondria.

10.3 Mitochondrial ROS and Longevity

Despite the general acceptance that mitochondrial dysfunction accelerates the aging process, there is not a clear consensus in the literature that this acceleration is mediated by increased mitochondrial ROS. The most compelling evidence supporting the notion that mitochondrial ROS regulates lifespan, as well as healthspan, comes from mice overexpressing a ROS-scavenging mitochondrial-targeted catalase. These mice, with reduced mitochondrial oxidative damage and mtDNA mutations and deletions, exhibit increased mean and maximal lifespan, as well as resistance to a number of age-related pathologies (Schriner et al. 2005; Dai et al. 2009; Treuting et al. 2008; Dai et al. 2014). Additionally, a noninvasive approach using the mitochondrial-targeted antioxidant SkQ1, has been shown to suppress cardiomyopathy and traits of aging and increase lifespan in mice (Anisimov et al. 2008, 2011; Dai et al. 2014; Manskikh et al. 2015; Skulachev et al. 2009). However, evidence against the pathologic role of mitochondrial ROS is provided by some early studies in ‘mutator mice’ harboring an exonuclease proofreading-deficient mitochondrial DNA polymerase gamma. Although these mice exhibited an accelerated aging phenotype driven by mtDNA mutations and deletions, they did not exhibit increased levels of ROS (Kujoth et al. 2005; Vermulst et al. 2008; Trifunovic et al. 2005; Hiona et al. 2010). However, recent studies using more sensitive approaches did detect increased mitochondrial ROS and oxidative damage in ‘mutator mice’ (Kolesar et al. 2014; Logan et al. 2014). In support of mitochondrial ROS as a driver of pathologic effects in this model, overexpression of mitochondrial-targeted catalase in ‘mutator mice’ alleviated mtDNA deletions, mitochondrial oxidative damage, and age-dependent cardiomyopathy (Dai et al. 2010, 2014). Additionally, antioxidant treatment attenuated somatic progenitor cell mtDNA mutagenesis and loss of self-renewal capacity in ‘mutator mice’ (Ahlqvist et al. 2012). These studies support the role of mitochondrial ROS as a driver of mitochondrial dysfunction and aging.

10.4 Mitochondrial ROS as an Inducer of Senescence

Although it is currently debated whether and how mitochondrial-derived ROS serves as an inducer of senescence, senescence induction by ROS is clear. ROS has been identified as a key player in establishing replicative, genotoxic stress and oncogene-induced senescence (Lu and Finkel 2008; Nair et al. 2015; Colavitti and Finkel 2005). In addition, exposure to exogenous hydrogen peroxide induces senescence through mechanisms involving genomic DNA damage (Duan et al. 2005; von Zglinicki et al. 2005; Borodkina et al. 2014), transforming growth factor-β (TGF-β) (Frippiat et al. 2001; Yu et al. 2009; Hassona et al. 2013), and $p38^{MAPK}$ signaling (Frippiat et al. 2002; Zdanov et al. 2006; Barascu et al. 2012; Iwasa et al. 2003). The generation of intracellular ROS appears to be a much earlier event than the onset of other senescent phenotypes as shown in a time-progression analysis of replicative senescence in human fibroblast (Kim et al. 2013). A significant increase in mitochondrial superoxide anion has been reported with increasing population doublings and replicative senescence in human fibroblasts, mesenchymal stem cells and vascular smooth muscle cells (Passos et al. 2007, 2013; Bielak-Zmijewska et al. 2014; Estrada et al. 2013; Nacarelli et al. 2015; Lerner et al. 2013). The mitochondria undergo distinct changes that may support the production of ROS during the induction of senescence. For instance, increased mitochondrial respiration has been detected in replicative, oxidative stress, and oncogene-induced senescence (Hutter et al. 2004; Kaplon et al. 2013; Quijano et al. 2012; Nacarelli et al. 2015). Not only are mitochondria the suspected culprits in the generation of ROS in promoting senescence, but also the immediate target. In replicative senescence of human fibroblasts, the most evidence of ROS-induced oxidative damage was detected within the mitochondria (Ahmed et al. 2010). This preferential accumulation of oxidative damage not only suggests that the mitochondria are a ROS source and target, but also that mitochondria are subject to reduced quality control in senescence.

Several studies have highlighted mitochondrial ROS in altering susceptibility to senescence. HIV highly active antiretroviral therapy nucleoside reverse transcriptase inhibitors (NRTIs), which are known to insult the mitochondria as an off-target effect and increase susceptibility to the development of age-related pathologies, increase ROS and induce senescence in human fibroblasts (Caron et al. 2008; Nacarelli et al. 2015). Mice deficient for the mitochondrial superoxide anion-scavenger MnSOD are more susceptible to oxidative stress and a range of age-related pathologies, and exhibit an abbreviated lifespan. In vivo and in vitro studies in these mice show evidence of increased vulnerability to oxidative stress-induced senescence (Velarde et al. 2012; Treiber et al. 2011). Contrary to the idea that MnSOD promotes longevity, overexpression of MnSOD fails to increase lifespan in mice (Jang and Van Remmen 2009). This is not surprising since overexpressing MnSOD may generate more hydrogen peroxide that will serve as a precursor for more harmful ROS (MacMillan-Crow and Crow 2011). Interestingly, 'mutator mice' exhibit increased p16 expression in their hearts. Remarkably, overexpressing

the mitochondrial-targeted catalase in these mice reduces expression of p16 in their heart, attenuating their age-dependent cardiomyopathy (Dai et al. 2010). It is possible that the mitochondrial-targeted catalase alleviates mitochondrial oxidative stress that induces senescence and contributes to the pathologic phenotype of cardiomyopathy.

10.5 ETC Dysfunction in Generating Mitochondria ROS

Given a severe insult, mitochondria can produce enough ROS to cause genomic instability and telomere attrition, providing a setting conducive for senescence (Liu et al. 2002). Disrupting the mitochondrial ETC and oxidative phosphorylation by severely uncoupling the proton gradient using *p*-trifluoromethoxyphenylhydrazone (FCCP) to produce high levels of mitochondrial ROS accelerates telomere attrition and induces oxidative stress-induced senescence in human fibroblasts (Stockl et al. 2007). Supporting a role for mitochondrial-generated ROS in replicative senescence, mild uncoupling to lower mitochondrial ROS reduced the rate of telomere shortening and extended replicative lifespan in human fibroblasts. The fact that the mitochondrial-targeted antioxidant mitoquinone (mitoQ) yielded the same effect in human fibroblasts pinpoints mitochondrial ROS as a factor in replicative senescence (Saretzki et al. 2003; Passos et al. 2007). Mild uncoupling of the mitochondria to reduce mitochondrial ROS was able to protect against hydrogen peroxide-mediated oxidative stress-induced senescence in human fibroblasts (Cho et al. 2014). This approach appears to be therapeutic at the organismal level, as mildly uncoupling mitochondria reduced mitochondrial ROS and oxidative damage in various tissues and extended lifespan in mice (Caldeira da Silva et al. 2008). One may speculate whether senescence was alleviated within the tissues of these mice during physiologic aging.

Besides uncoupling, direct damage to the ETC can lead to the production of mitochondrial superoxide anion from complexes I and III. Indeed, inhibiting complex I using rotenone or complex III using antimycin A increased mitochondrial ROS and induced senescence in human fibroblasts (Velarde et al. 2012; Moiseeva et al. 2009; Stockl et al. 2006). Additionally, disrupting complex I by silencing its assembly factor NDUFAF1 increased mitochondrial ROS and induced senescence in human fibroblasts. Supporting a role in longevity, efficient assembly of complex I is associated with lower ROS levels and a feature of young, rapamycin-fed, and long-lived mice (Miwa et al. 2014). The ETC can also be altered in response to signaling to provoke the generation of mitochondrial ROS that induces senescence. For instance, the senescence-promoting proinflammatory cytokine transforming growth factor-β1 inactivates glycogen synthase kinase 3 to suppress complex IV activity of the ETC that results in the generation of mitochondrial ROS and induction of senescence (Byun et al. 2012). Another cascade in mitochondrial ROS-induced senescence is in response to angiotensin II-mediated NADPH oxidase activation in vascular smooth muscle cells. Activation of NADPH oxidase by angiotensin

II elicits a feed-forward mechanism where the production of superoxide anion from the mitochondria further activates NADPH oxidase and causes senescence. Suppressing mitochondrial ROS in this setting by mild inhibition of complex I using rotenone or a mitochondrial-target antioxidant prevented this cross-talk and senescence (Mistry et al. 2013).

10.6 Impaired Mitochondrial Dynamics in Generating Mitochondrial ROS

Mitochondria are dynamic organelles that continually undergo fusion and fission events to alter their morphology and organization. These processes, which are required for maintenance and quality control of the mitochondria, facilitate the degradation of dysfunctional mitochondria through autophagy, a process termed mitophagy. Altering mitochondrial fission has been shown to impact ROS levels and senescence (Seo et al. 2010). Inhibiting mitochondrial fission by knocking down fission protein 1 (Fis1) caused mitochondrial elongation, increased ROS levels, DNA damage, and senescence (Lee et al. 2007). Similar effects were observed when mitochondrial fusion and enlargement were aberrantly stimulated using deferoxamine (Yoon et al. 2006). Likewise, enlarged mitochondrial morphology has been observed in replicative senescence (Hwang et al. 2009). Senescence has also been studied in response to mitochondrial insults that impair dynamics. Disruption of mitochondrial dynamics and mitochondrial fragmentation induced by cigarette smoke extract increased mitochondrial ROS and induced senescence. Mitochondrial ROS appeared to be required for the induction of senescence in this setting, as these responses were prevented in the presence of a mitochondrial-targeted antioxidant (Hara et al. 2013). Mitochondrial ROS-induced senescence in response to cigarette smoke extract was also ameliorated when mitophagy was stimulated to remove dysfunctional mitochondria (Ito et al. 2015). These studies highlight the importance of quality control to eliminate aberrant mitochondria with the potential to increase ROS and put the cells at risk for senescence.

10.7 Metabolic Disruption in Promoting Mitochondrial ROS

Increased mitochondrial ROS in the induction of senescence has been studied in regards to glucose metabolism. Although senescent cells are metabolically active, the glycolytic status within senescent cells is unclear. Increased glycolysis has been reported in replicative and radiation-induced senescent cells (Bittles and Harper 1984; Goldstein et al. 1982; Liao et al. 2014; James et al. 2015). However, oncogene-induced senescence is characterized by a metabolic shift from glycolysis to the TCA cycle due to decreased expression of glycolytic proteins and increased

pyruvate oxidation (Kaplon et al. 2013; Li et al. 2013a). Exposing cells to a high concentration of glucose increased mitochondrial ROS and caused oxidative stress-induced senescence (Ksiazek et al. 2008; Park et al. 2014). Unfortunately, these studies did not address whether high glucose aberrantly stimulated glycolysis or had a direct effect on the mitochondria. Similarly, supplying the cell with excessive TCA cycle intermediates by overexpressing sodium-dependent dicarboxylate cotransporter 3, disrupted mitochondrial ETC activity, increased ROS levels, and caused oxidative stress-induced senescence in human fibroblasts (Ma et al. 2014). Interestingly, high levels of the TCA cycle intermediate fumarate lowered antioxidant defenses by inactivating glutathione and caused oxidative stress-induced senescence (Zheng et al. 2015). These results support the idea that an altered metabolism or altered levels of metabolites are capable of damaging mitochondria and increasing ROS to induce senescence. Of course it is possible that mitochondrial dysfunction alters glucose metabolism in a way that promotes the generation of mitochondrial ROS. For instance, it is suspected that mitochondrial dysfunction accounts for transcriptional and metabolic changes in the TCA cycle during replicative senescence in *Saccharomyces cerevisiae* (Kamei et al. 2014).

10.8 Senescence Induction of Mitochondrial ROS: p53 Effector Response

Although discussed up to this point as an upstream effector of senescence, elevated mitochondrial ROS might also represent a downstream mechanism to maintain the senescence phenotype. Senescence induction by the p53/p21 pathway as part of the DNA damage response increased and sustained ROS production from the mitochondria, forming a positive feedback mechanism, whereby further DNA damage and p53/p21 pathway activation served to maintain senescence (Passos et al. 2010). p53 can serve as a major effector in establishing high levels of ROS following senescence induction, by altering mitochondria redox status. Elevated p53 can transcriptionally downregulate mitochondrial MnSOD, the mitochondrial antioxidant that dismutates mitochondrial superoxide anion into hydrogen peroxide. Also, MnSOD ROS-scavenging activity can be impaired by physical interaction with p53 following localization of p53 to the mitochondria (Lebedeva et al. 2009; Pani and Galeotti 2011). p53 also serves a mitochondrial pro-oxidant role by promoting p66Shc, which translocates to the mitochondria and generates ROS by transferring electrons from cytochrome c to molecular oxygen (Pani and Galeotti 2011; Galimov et al. 2014; Giorgio et al. 2005). p66Shc also is responsive to ROS and has been shown to increase at the mRNA and protein level during oxidative stress-induced senescence in fetal bovine fibroblasts (Favetta et al. 2004). Suggesting a role in longevity, mice deficient for p66Shc are less susceptible to oxidative stress and age-related pathologies (Migliaccio et al. 1999; Berry and Cirulli 2013). These mice accumulate fewer senescent cells in their thymus during physiological aging,

and embryonic fibroblasts from these mice are resistant to oxidative stress-induced senescence, further supporting the notion that these mice are protected against oxidative stress (Gambino et al. 2013). Mitochondrial autophagy and dynamics can also be impaired by p53, leading to the generation of mitochondrial ROS. For instance, in replicatively senescent mouse embryonic fibroblasts, cytosolic p53 prevents mitochondrial localization and action of parkin, an E3 ubiquitin ligase that facilitates autophagic clearance of dysfunctional mitochondria (Hoshino et al. 2013).

10.9 Senescence Induction of Mitochondrial ROS: Metabolic Disruption

Oncogene-induced senescence is also triggered by a p53 response that promotes the production of mitochondrial ROS. For example, ras-mediated oncogene-induced senescence entails p53-dependent mitochondrial dysfunction that is defined by increased mitochondrial mass and production of superoxide anion in human fibroblasts (Moiseeva et al. 2009; Lee et al. 1999). Supporting the notion of altered mitochondrial function, ras-mediated senescence increases the rate of mitochondrial respiration and the proteins that support this, particularly mitochondrial pyruvate dehydrogenase (Quijano et al. 2012; Li et al. 2013a). Pyruvate dehydrogenase has also been identified as a key factor in mediating increased mitochondrial respiration and ROS in oncogenic $BRAF^{V600E}$-induced senescence. This senescent phenotype was maintained by elevated pyruvate dehydrogenase activity, which increased pyruvate oxidation and sustained a high level of mitochondrial respiration (Kaplon et al. 2013). Interestingly, pyruvate dehydrogenase, itself, is capable of generating ROS from the mitochondria (Quinlan et al. 2014). It is currently unknown whether pyruvate dehydrogenase activity is increased in replicative and oxidative stress-induced senescence. Mitochondrial metabolism might also become dysregulated in such a way that increases ROS in senescent cells through feedback between p53 and the mitochondrial $NAD(P)^+$-dependent malic enzyme (ME2). Through oxidative decarboxylation of malic acid into pyruvate within the mitochondria, ME2 replenishes the mitochondrial NADPH pool that is required by endogenous mitochondrial antioxidants. ME2 can be transcriptionally repressed by p53, leading to elevated levels of ROS that activate p53 in an AMPK-dependent manner. Since ME2 reciprocally represses p53, knocking down ME2 induces p53-dependent senescence (Jiang et al. 2013; Korge et al. 2015). It is unclear whether increased mitochondrial ROS in these settings serves as a driver in sustaining the senescent phenotype, rather than an effect. Nonetheless, it is evident that an altered mitochondrial function that supports the production of ROS is a part of the metabolic phenotype of senescent cells.

10.10 Mitochondrial ROS Interventions for Suppressing Cellular Senescence

Given its impact on senescence, mitochondrial ROS could be targeted as a strategy to provide longevity assurance. The most direct strategy might make use of the aforementioned mitochondrial-targeted antioxidants. However, the most effective and long-term intervention would be an intervention that improves mitochondrial homeostasis and provides resistance against mitochondrial stress. Our laboratory has shown that senescence is delayed and replicative lifespan is increased in human fibroblasts treated long term with 1 nM rapamycin, a pharmacologic inhibitor of mTORC1. Notable features of these rapamycin-treated cells included improved mitochondrial homeostasis and diminished ROS (Lerner et al. 2013). Other studies have also highlighted the suppression of senescence by rapamycin (Demidenko et al. 2009; Pospelova et al. 2012). Rapamycin treatment also provides resistance to mitochondrial insults, such as ethidium bromide or NRTI treatment, which increase ROS levels and susceptibility to senescence (Nacarelli et al. 2014, 2015). These results may help to explain the benefits of rapamycin in slowing aging and extending organismal lifespan among various species, and protecting against age-related pathologies in disease mouse models (Johnson et al. 2013; Ehninger et al. 2014). Rapamycin is thought to converge on similar longevity-extending pathways as caloric restriction, a well-known intervention that also improves mitochondrial function, and protects against age-related diseases (Colman et al. 2009; Bratic and Larsson 2013).

Interestingly, at least some aspects of the longevity features and benefits of caloric restriction can be obtained through restricting the amino acid L-methionine in rodents. A targeted reduction of methionine synthase to reduce methionine levels has also been shown to extend lifespan and increase stress resistance in *S. cerevisiae* and human fibroblasts (Johnson and Johnson 2014). A major effect of L-methionine restriction appears to be the reduction of mitochondrial ROS generation and oxidative stress (Sanchez-Roman and Barja 2013). Remarkably, restricting L-methionine in cell culture media suppressed the generation of mitochondrial ROS and oxidative damage, delayed senescence, and extended replicative lifespan in human fibroblasts (Koziel et al. 2014). These interventions provide mechanistic insight into how improving mitochondrial homeostasis and sustaining low levels of mitochondrial ROS could support longevity pathways and delay senescence.

10.11 Conclusion

Mitochondria maintain cellular homeostasis and are critical determinants of cellular longevity. One detrimental effect of mitochondrial dysfunction is the generation of superoxide anion, which gives rise to high levels of ROS. High levels of ROS

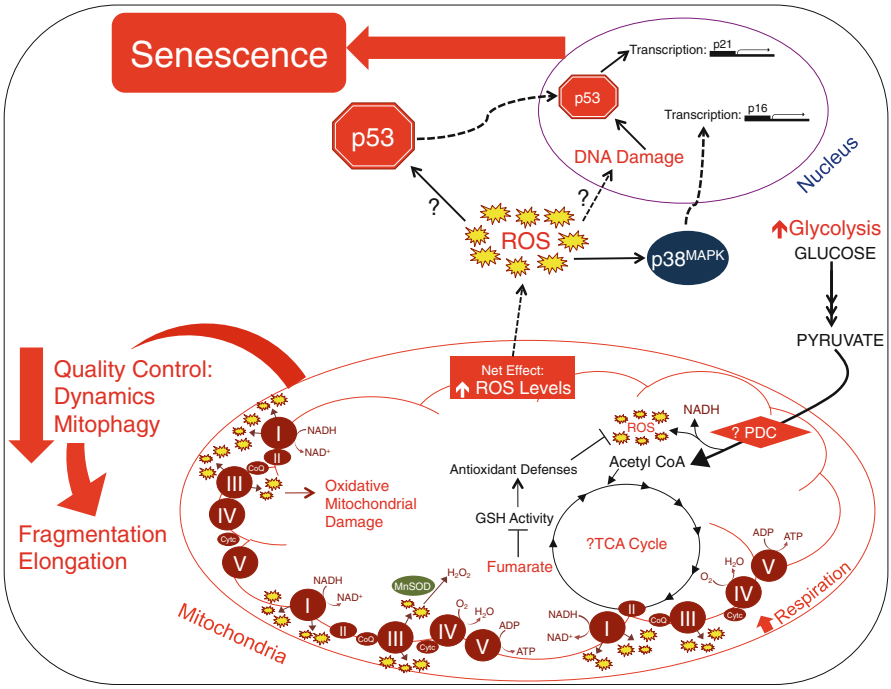

Fig. 10.1 Mitochondrial ROS as an inducer of senescence. Synthesis of events that increase mitochondrial ROS in the induction of cellular senescence

damages macromolecules and establish a stressful cellular environment. This stress stimulus may induce senescence, promoting aging. In Figs. 10.1 and 10.2, we put forth a synthesis of the mechanisms by which mitochondrial ROS initiates or helps maintain senescence. Alterations in the mitochondria that support the generation stress-inducing ROS include ETC dysfunction, altered dynamics that impair quality control, and metabolic disruption. Given a non-mitochondrial stimulus, senescent cells can also generate signals as a mechanism to maintain the senescence phenotype to induce mitochondrial ROS. This encompasses effector responses of p53 and changes in metabolism. Various interventions that alleviate increased mitochondrial ROS levels, such as rapamycin treatment or methionine restriction, might be effective in preventing senescence and extending longevity. These methods might succeed in preventing cascades initiated, amplified, or maintained by mitochondrial ROS in promoting senescence. Although senescence is irreversible, these interventions may also assist in confining the pathological effects of senescent cells through a reduction in SASP, the senescence-associated secretory phenotype that acts to

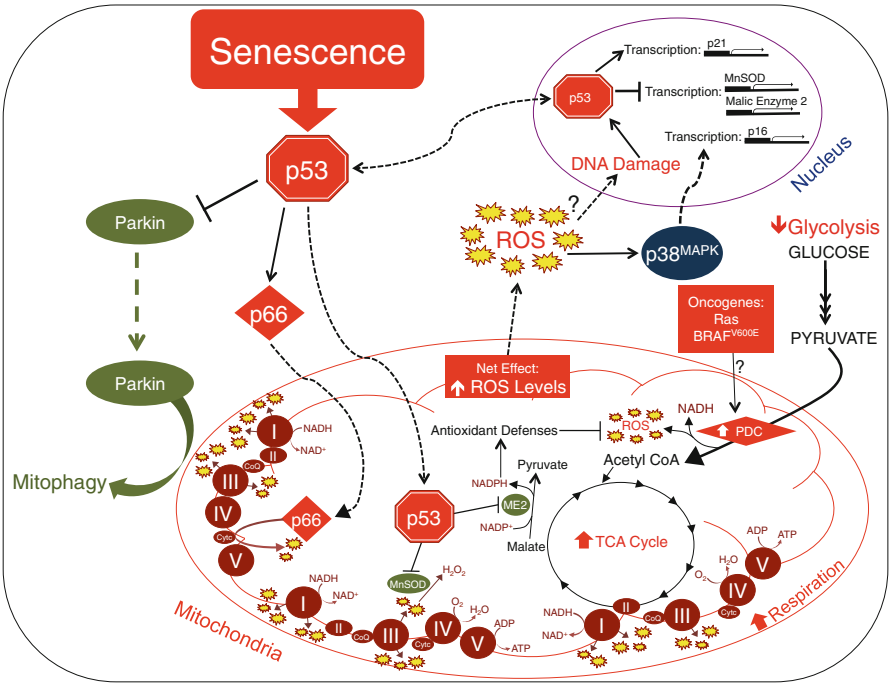

Fig. 10.2 Senescence induction of mitochondrial ROS. Synthesis of events mediating increased levels of mitochondrial ROS following the induction of cellular senescence

promote a pro-inflammatory state. With mitochondrial ROS being a common target, these therapeutic approaches are important in understanding age-promoting stress signaling and ways to decelerate senescence.

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