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Healthful Aging Mediated by Inhibition of Oxidative Stress

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Abstract

The progressive increase in lifespan over the past century carries with it some adversity related to the accompanying burden of debilitating diseases prevalent in the older population. This review focuses on oxidative stress as a major mechanism limiting longevity in general, and healthful aging, in particular. Accordingly, the first goal of this review is to discuss the role of oxidative stress in limiting longevity, and compare healthful aging and its mechanisms in different longevity models. Secondly, we discuss common signaling pathways involved in protection against oxidative stress in aging and in the associated diseases of aging, e.g., neurological, cardiovascular and metabolic diseases, and cancer. Much of the literature has focused on murine models of longevity, which will be discussed first, followed by a comparison with human models of longevity and their relationship to oxidative stress protection. Finally, we discuss the extent to which the different longevity models exhibit the healthful aging features through physiological protective mechanisms related to exercise tolerance and increased β-adrenergic signaling and also protection against diabetes and other metabolic diseases, obesity, cancer, neurological diseases, aging-induced cardiomyopathy, cardiac stress and osteoporosis.

Keywords

Healthful Longevity; Oxidative Stress; Reactive Oxygen Species

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DISCLOSURES

None

I. Introduction

There has been a progressive increase in lifespan over the past century. At the turn of the 20th century the average lifespan was 48 years for men and 51 years for women. More than 100 years of progress has led to a life expectancy of 76 years for men and 81 years for women as of 2017 (Xu, Murphy et al. 2020). Prima facie, these data are encouraging, as almost everyone wishes to live longer. However, an extended lifespan carries with it the burden of concomitant debilitating diseases and accompanying morbidity, which limit ambulation and enjoyment of life. It is important to recognize that most of these diseases are mediated, in part, by increased oxidative stress (Beck 2000, Cervantes Gracia, Llanas-Cornejo et al. 2017, Guzik and Touyz 2017, Butterfield and Halliwell 2019, Goncalves and Romeiro 2019, Hosseinabadi and Khanjani 2019, Katerji, Filippova et al. 2019, Gyuraszova, Gurecka et al. 2020, Zhang, Li et al. 2020). Oxidative stress is thought to be a major mechanism limiting longevity in general (Finkel and Holbrook 2000, Yoon, Yun et al. 2002), and limiting healthful longevity, in particular, which has not been examined in depth. Accordingly, the first goal of this review is to discuss the role of oxidative stress in limiting healthful longevity. The second goal is to discuss the extent to which the different longevity models are protected against the associated disabling diseases of aging, e.g., diabetes and other metabolic diseases, obesity, cancer, neurological disorders, aging-induced cardiomyopathy, cardiac stress, osteoporosis, reduced exercise tolerance and increased β-adrenergic signaling.

II. Oxidative Stress in Aging

Oxidative stress impairs healthful aging (Szilard 1959), and accordingly, protection against oxidative stress is a common mechanism mediating the phenotype observed in animal models of longevity (Table I). Reactive oxygen species (ROS) are mainly a byproduct of oxygen metabolism and adenosine triphosphate (ATP) production. When ROS exceed antioxidant capacity, as occurs with radiation exposure, high fat diet, sugar, processed foods, cigarette smoking, other tobacco products, alcohol consumption, certain medications, pollution, exposure to pesticides or industrial chemicals, they induce oxidative stress that is directly linked to the development of many diseases that limit healthful aging (Valko, Leibfritz et al. 2007, Alfadda and Sallam 2012). A major mechanism by which oxidative stress causes tissue damage is through ROS induced apoptosis and necrosis by opening of the mitochondrial membrane permeability transition pore and releasing factors which limit cell survival, such as cytochrome c (Wei and Lee 2002). In order to maintain cellular equilibrium, mammalian cells scavenge ROS to nontoxic forms through a complex antioxidant defense system that includes superoxide dismutase (SOD), catalase, and glutathione peroxidase (Gpx) (Wei and Lee 2002, Valko, Leibfritz et al. 2007, Alfadda and Sallam 2012). Several cellular/biochemical signaling mechanisms mediate increase oxidative stress in aging; one mechanism is a decrease in mitochondrial efficiency, resulting increased ROS production, in order to maintain sufficient ATP production. The significance of the mitochondria in aging arises from their particular susceptibility to DNA damage. Most of an organism’s DNA is stored in the cell’s nucleus which, because of its membrane, is more protected from DNA damage by free radicals. The mitochondrial DNA (mtDNA) located within mitochondria, lacks protection provided by the nucleosomes and DNA repair

mechanisms; which makes mtDNA highly susceptible to oxidant induced damage during aging (Mikhed, Daiber et al. 2015). ROS also play a vital role in several physiological functions as a second messenger and are critical in neutrophil function, impairing the host defense against micro-organisms and in the innate immune response. Neutrophils express and release cytokines, which in turn, amplify inflammatory reactions in several other cell types (Winterbourn, Kettle et al. 2016). Furthermore, similar to ROS, free-radicals also result in oxidative stress (Lobo, Patil et al. 2010), and the activity of free-radical scavenging enzymes diminishes with advancing age and contributes to the adverse effects of oxidative stress with aging (Inal, Kanbak et al. 2001).

There are genetically modified animal models designed to help elucidate the role of the antioxidant system. Manganese superoxide dismutase (MnSOD), which is also known as superoxide dismutase 2 (SOD2), is one of the main mitochondrial antioxidant proteins. The genetic ablation of SOD2 leads to early postnatal death in mice which exhibit a dilated cardiomyopathy, metabolic acidosis, steatosis of the liver and skeletal muscle, increased oxidative damage, and mitochondrial enzymatic abnormalities (Li, Huang et al. 1995, Melov, Coskun et al. 1999). Partial loss of SOD2 (SOD2 heterozygous mice) also induces increased oxidative stress (Kokoszka, Coskun et al. 2001). Treatment of SOD2 knockout (KO) mice with a synthetic SOD mimetic rescues their mitochondrial defects and prolongs their survival (Melov, Schneider et al. 1998). Other KO mice for other antioxidant proteins, e.g., Cu/Zn SOD or SOD1, also exhibit increased oxidative damage of DNA, lipid peroxidation, and an increase in mitochondrial aconitase, which is a biomarker of oxidative stress (Elchuri, Oberley et al. 2005). In contrast, mice with SOD1 overexpression tend to be more resistant to paraquat induced oxidative stress (Mele, Van Remmen et al. 2006). Similarly, investigations of other antioxidants, such as catalase, show that increasing the body’s defense against free radicals can extend life (Table I).

In summary, the mechanism of oxidative stress induced in aging is multifactorial, with mitochondrial damage playing a significant role. The final common pathway for premature cell death involves apoptosis, necrosis, and cell cycle arrest (Slater, Stefan et al. 1995, Sastre, Pallardo et al. 2003, Barzilai and Yamamoto 2004), all of which induce cell death (Choi, Kim et al. 2001, Yuan, Long et al. 2012) (Figures 1 and 2).

III. Common Signaling Pathways Involved in Oxidative Stress Protection (Figure 2):

The major mechanisms mediating protection against oxidative stress are noted in Figure 2 and are discussed next. Many, but not all, of these mechanisms mediating oxidative stress protection are involved in each model of longevity with oxidative stress protection. These are the major mechanisms that lead to reduced oxidative stress, enhanced mitochondrial function and reduced apoptosis and cell death, ultimately culminating in protection against most diseases, which increase morbidity and mortality in the aging population.

Mitogen-Activated Protein Kinase (MAPK) Signaling Pathways:

Activator protein-1 (AP-1) activity is regulated by a variety of stimuli, which include oxidative stress and signals through the MAPK cascades leading to extracellular signal-related kinases (ERKs), c-jun NH2-terminal kinases (JNKs) and p38 MAPK. These pathways are known to be influenced not only by receptor ligand interactions, but also by different stressors placed on the cell. One type of stress that induces activation of MAPK pathways is the oxidative stress caused by ROS, which in turn activate the Proto-Oncogene, Serine/Threonine Kinase (Raf)/MEK/ERK, JNKs, or p38 MAPKs (Son, Cheong et al. 2011).

Phosphoinositide 3-Kinases (PI3K)/ Protein Kinase B (Akt) Pathway:

Oxidative stress activation of the PI3K/Akt pathway targets the nuclear factor kappa-light-chain-enhancer of the activated B cells (NF-κB) site in the SOD1 promoter, resulting in upregulation of SOD1 gene expression that lowers ROS levels and protects cells against oxidative stress (Noshita, Sugawara et al. 2003, Rojo, Salinas et al. 2004). The inhibition of Akt activation reduces production of superoxide and SOD1 levels (Song, Narasimhan et al. 2008). Aberrant PI3K/Akt signaling drives many of the molecular mechanisms to increase ROS levels by modulation of mitochondrial bioenergetics and activation of NADPH oxidases (Murphy 2009). NADPH oxidases activated by PI3K/Akt contribute to higher ROS levels in cancer cells (Chatterjee, Browning et al. 2012). The Forkhead box O (FoxO) family is an important regulator of the cellular stress response and is involved in the cellular antioxidant defense, and is downstream of the PI3K/Akt pathway (Brunet, Bonni et al. 1999, Martins, Lithgow et al. 2016). Phosphorylation of FoxOs induced by PI3K/Akt stimulates and regulates the transcription and expression of antioxidant enzymes in mitochondria and plasma, e.g., MnSOD, catalase, thioredoxin and stress-related gene products (Nemoto and Finkel 2002, Tran, Brunet et al. 2003, Olmos, Sanchez-Gomez et al. 2013). FoxOs also regulate the expression of ROS scavengers in response to ROS (Kops, Dansen et al. 2002, Nemoto and Finkel 2002). Reduced expression of FoxO transcription factors increase susceptibility to cell death induced by oxidative stress (Akasaki, Alvarez-Garcia et al. 2014). In addition, transcriptional and post-transcriptional control of FoxO gene expression is sensitive to ROS (Klotz, Sanchez-Ramos et al. 2015). Oxidative stress mediated by ROS is a key mediator of the acetylation and ubiquitination state of FoxOs (Brunet, Sweeney et al. 2004, Frescas, Valenti et al. 2005, Dansen, Smits et al. 2009).

Heat Shock Proteins:

Heat shock proteins are induced by a family of heat shock transcription factors and are known for their cytoprotective role in response to a variety of cellular insults through their chaperoning activities, which include protein folding, assembly, and the degradation of irreparable peptides (Mayer and Bukau 2005, Shiber and Ravid 2014). DNA fragmentation is induced in cells undergoing ROS-mediated genotoxicity, but this effect is rescued with the addition of the Hsp70 family suggesting that the cytoprotective effects of heat shock proteins protect against DNA breaks in response to ROS-induced insults (Jacquier-Sarlin, Fuller et al. 1994). Heat shock proteins work hand-in-hand with the antioxidant system to inhibit or neutralize the cellular effects of ROS (Trott, West et al. 2008, Wu, Biggar et al. 2015).

Several studies investigated the role of heat shock proteins in reducing oxidative stress by increasing ROS scavenger genes (Wyttenbach, Sauvageot et al. 2002, Driedonks, Xu et al. 2015, Ghosh, Sarkar et al. 2018).

p53:

P53 is a tumor suppressor protein and regulates the expression of genes involved in cell cycle regulation, redox homeostasis, DNA replication and repair, autophagy, and apoptosis (Levine, Feng et al. 2006, Holley and St Clair 2009, Saleem, Adhihetty et al. 2009). In addition, p53 is also an important regulator of mitochondrial biogenesis (Yoshida, Izumi et al. 2003, Saleem, Adhihetty et al. 2009). This is observed in p53 KO mice, which have impaired mitochondrial function and elevated ROS (Saleem, Adhihetty et al. 2009). Furthermore, p53 has dual roles with respect to mediating oxidative stress. Under no oxidative stress or low oxidative stress conditions, p53 and its negative regulators are post-translationally modified, and lead to p53 activation, which provides an antioxidant defense (Liu and Xu 2011). For example, fasting from calorie restriction induced oxidative stress, activates p53 to enhance both antioxidant production and fatty acid oxidation mechanisms to reduce the overall oxidative stress (Beyfuss and Hood 2018). In contrast, under conditions of severe oxidative stress, p53 is activated to induce pro-oxidant genes and inhibit antioxidant genes to further increase ROS levels and sensitize cells to oxidative stress, which will then eliminate damaged cells via p53- dependent apoptosis and senescence. (Johnson, Yu et al. 1996, Donald, Sun et al. 2001, Drane, Bravard et al. 2001).

NF-κB:

NF-κB plays a protective role in response to oxidative stress by suppressing ROS accumulation (Lingappan 2018). One of the main signaling pathways that intersects with NF-κB related to ROS and cell death is the crosstalk that occurs between NF-κB and JNK (Morgan and Liu 2011). Decreases in NF-κB-mediated inhibition of JNK activation contributes to TNF-alpha-induced apoptosis (Tang, Tang et al. 2002). Thus, the anti-apoptotic function of NF-κB is also mediated by downregulation of the JNK pathway. NF-κB also has many anti-oxidant targets such as MnSOD, Glutathione S-transferase pi, Metallothionein-3, NAD(P)H dehydrogenase [quinone]1, heme oxygenase-1 and Gpx-1 (Kairisalo, Korhonen et al. 2007, Morgan and Liu 2011). The NF-κB pathway also has a pro-oxidant role by induction of genes such as NADPH oxidase 2 (NOX2) subunit gp91phox (Anrather, Racchumi et al. 2006).

IV. Oxidative Stress in Longevity Models

To further understand the importance of protection against oxidative stress in aging, the major longevity models and their relation to oxidative stress protection are enumerated in Table I followed by a description of the animal and human longevity models.

Longevity Animal Models (Tables I and II)

Most longevity models have evidence of protection against oxidative stress. Accordingly, this section and Table I are divided into those longevity models with known oxidative stress protection, those longevity models lacking such protection, and models where protection is

controversial or has not been studied. Table I is organized by listing the longevity models from those with longest % increase in median survival, compared to their wild type (WT) littermates, to those with the least. This section and Table I include the median age of survival in the longevity models and the median age of survival in their WT littermates. Table II compares the protective features, observed in healthful aging, in these longevity models. The data for this review were collected by examining the literature for all longevity models and then determining whether they are protected from oxidative stress and those mechanisms and diseases that involve oxidative stress and the morbidity and mortality that limit healthful longevity.

Limitations of Longevity Models

Many longevity models discussed below only reflect longevity compared to their WT, and not compared with most mouse strains studied. When evaluating the differences in lifespan of mice from different genetic backgrounds, it is also necessary to understand the inherent differences in lifespan of the background inbred strains of mice that are used. Some of the most commonly used inbred strains include C57BL/6, BALB/c, and DBA/2J (Overbeek 2014). These mice exhibit differences in their median lifespan. For example, male and female BALB/cJ mice have a median lifespan of 19 and 18 months respectively, whereas male and female C57BL/6J male mice have a median lifespan of 22 and 21 months respectively, while both male and female DBA/2J male mice have a median lifespan of 22 months (Storer 1966).

Both molecular and environmental factors affect lifespan. For example, it has been shown that differences in lifespan among strains may be due to the plasma IGF1 level, which has been shown to be negatively correlated with median lifespan (Yuan, Tsaih et al. 2009). IGF1 is also known as an important regulator of longevity in transgenic mice, including Ames Dwarf mice, GHR KO mice, p66shc KO mice, and IGF-1R$^{+/-}$ mice (Brown-Borg, Borg et al. 1996, Migliaccio, Giorgio et al. 1999, Coschigano, Holland et al. 2003, Holzenberger, Dupont et al. 2003). Lifespan may also be affected by the environment, e.g. housing conditions. The median lifespan from some WT strains may vary among different studies, e.g., median lifespan of C57BL/6J mice was reported as 21–22 months in one study (Storer 1966), and 28–29 months in another study (Yuan, Tsaih et al. 2009). In our laboratory, we found the median lifespan of this strain to be around 24–25 months (Yan, Vatner et al. 2007). Another study showed that environmental enrichment, specifically auditory and acoustic stimulation, prolonged lifespan by roughly 17% in C57BL/6J mice (Yamashita, Kawai et al. 2018).

Thus, differences in longevity across transgenic models using different background inbred strains presents an additional layer of complexity in evaluating optimal models of longevity. Another limitation to mouse longevity studies is that in many of the longevity models there is a discrepancy between the average increase in lifespan compared to WT, depending on whether lifespan is evaluated by estimating median lifespan from the survival curve at 50% survival rate, *vs.* the longevity data noted in the publication (Schriner, Linford et al. 2005, Ortega-Molina, Efeyan et al. 2012). The reasons for these discrepancies are not clear. In addition, there are some mouse longevity models with increased average lifespan of males

and females less than 16%. These models are not discussed and include: 1) models that are protected against oxidative stress: sirtuin 1 overexpressed mice, metallothionein overexpressed mice; 2) models that are not protected against oxidative stress: α-murine urokinase-type plasminogen activator overexpressed mice, glutathione peroxidase 4 hetero KO mice; 3) models that have controversial data on protection against oxidative stress: macrophage migration inhibitory factor KO mice, fat-specific insulin receptor KO mice; and 4) models with oxidative stress not studied: sirtuin 6 overexpressed mice, RIIβ KO mice, phosphatase and tensin overexpressed mice, and hypocretin neurons-specific uncoupling protein 2 overexpressed mice (Miskin and Masos 1997, Bluher, Kahn et al. 2003, Conti, Sanchez-Alavez et al. 2006, Yang, Doser et al. 2006, Ran, Liang et al. 2007, Enns, Morton et al. 2009, Harper, Wilkinson et al. 2010, Kanfi, Naiman et al. 2012, Ortega-Molina, Efeyan et al. 2012, Satoh, Brace et al. 2013, Steckler, Shabtay-Yanai et al. 2016).

(1) Longevity Models with Known Protection Against Oxidative Stress:

Calorie Restriction in Mice (Median Age of Survival of Calorie Restriction is Increased up to 50% Compared to Normal Diet Median Age of Survival of 30 Months): Calorie restriction, extends lifespan up to 50% in rodents (McCay, Crowell et al. 1989, Fontana, Partridge et al. 2010) and generally ameliorates disease in mammals (Fontana, Partridge et al. 2010). The effect on lifespan with calorie restriction may vary by sex and genetic background in rodents (Liao, Rikke et al. 2010). The majority of studies showed calorie restriction leads to enhanced mitochondrial biogenesis and function as well as lower ROS production and greater antioxidant enzyme activity in wild-type mice (Sohal, Ku et al. 1994, Lopez-Lluch, Hunt et al. 2006, Swindell 2009, Qiu, Brown et al. 2010, Martin-Montalvo, Villalba et al. 2011, Chen, Hagopian et al. 2012, Donato, Walker et al. 2013, Walsh, Shi et al. 2014, Mitchell, Delville et al. 2015, Noyan, El-Mounayri et al. 2015) and in genetically altered mice (Harrison, Archer et al. 1984, Guo, Mitchell-Raymundo et al. 2002). However, differences in oxidative stress levels among different organs exists with calorie restriction (Sohal, Agarwal et al. 1994, Gong, Shang et al. 1997, Rebrin, Kamzalov et al. 2003, Rebrin, Forster et al. 2007, Walsh, Shi et al. 2014), and differences have been noted that can be attributed to the duration of calorie restriction (Wu, Sun et al. 2003). There are even some studies that reported calorie restriction either reduced lifespan in wild-type mice (Harrison and Archer 1987), or failed to further prolong lifespan in longevity mouse models (Bonkowski, Rocha et al. 2006, Bonkowski, Dominici et al. 2009). The most striking example is when calorie restriction was added to a mouse model of longevity, the AC5 KO mice. All the AC5 KO mice on a calorie restricted diet, that normally increases longevity, died within a month due to higher metabolism of the AC5 KO mice, which could not tolerate reduction in food intake, indicating that calorie restriction is deleterious in models of increased metabolism (Yan, Park et al. 2012).

Calorie Restriction Protects Against Cardiovascular Diseases: Long term calorie restriction can alter the gene expression profile related to protection against myocardial remodeling, fibrosis and decreases in contractility (Swindell 2009, Yan, Gao et al. 2013). Short term calorie restriction results in smaller myocardial infarct size, improved cardiac function and survival in mice with myocardial infarction, as well as enrichment of anti-oxidative stress pathways (Noyan, El-Mounayri et al. 2015). Calorie restriction also reduces

oxidative stress and atherosclerosis in genetically altered atherosclerosis mice (Guo, Mitchell-Raymundo et al. 2002, Yang, Zeng et al. 2020).

Calorie Restriction Protects Against Metabolic Diseases: Mice undergoing calorie restriction exhibit lower bodyweight (Schmeisser, Priebe et al. 2013), a reduction in body fat (Yan, Gao et al. 2013, Mitchell, Tang et al. 2015), and an improvement in glucose homeostasis with lower oxidative stress (Mitchell, Delville et al. 2015). In one study, calorie restriction also lowered fasting blood glucose levels in diabetic mice (Wei, Zhao et al. 2019). Furthermore, a recent metabolomics study demonstrated brown adipose tissue activation in mice with calorie restriction (Green, Mitchell et al. 2020). Brown adipose tissue is a novel mechanism of longevity and protection against oxidative stress (Vatner, Zhang et al. 2018) and also protects against obesity and diabetes (Stanford, Middelbeek et al. 2013).

Calorie Restriction Protects Against Cancer: The protective effects of calorie restriction on the incidence of cancer have been observed in numerous studies of spontaneous and chemically induced tumors in rodents (Weindruch, Walford et al. 1986, Hursting, Smith et al. 2010, Longo and Fontana 2010, De Lorenzo, Baljinnyam et al. 2011). Decreasing growth factor signaling as well as vascular perturbations and inflammation attenuates cancer risk and progression (Hursting, Dunlap et al. 2013). The model is further protected against cancer when calorie restriction is maintained throughout the entire lifespan compared to when initiated in adulthood (Hursting, Smith et al. 2010). Although the overall incidence of tumors is not reduced with calorie restriction later in life, tumorigenesis is delayed and survival is improved (Dhahbi, Kim et al. 2004). Calorie restriction prevents tumorigenesis by reducing metabolic rate and oxidative damage (Martin-Montalvo, Villalba et al. 2011). A review of rodent studies on cancer and calorie restriction revealed the protective role of calorie restriction against cancer in 40 out of 44 studies whereas only 4 studies reported negative or no difference results in mammary tumors (Tagliaferro, Ronan et al. 1996), prostate cancer (Birt, Pour et al. 1997, McCormick, Johnson et al. 2007), and intestinal tumors (Tsao, Dudley et al. 2002).

Non-human primate studies and human studies on calorie restriction are discussed in Sections VI and VII.

Snell Dwarf Mice (Median Age of Survival, of Snell Dwarf is Increased by 50% in Females, but Is Decreased in Males by 6% Compared to WT Median Age of Survival of 18 Months): Snell dwarf mice have a mutation in the gene encoding pituitary-specific positive transcription factor 1 (Pit-1) and result in an altered hormone profile featuring primary deficiencies in growth hormone, thyroid-stimulating hormone, and prolactin and thus secondary deficiencies in insulin-like growth factor 1 and thyroxine (Bartke and Brown-Borg 2004). They exhibit longevity compared to their WT, with gender differences also apparent. In females, maximal lifespan is increased by 38% and median lifespan is increased by 50%; whereas in males, maximal lifespan is increased by 25% but median lifespan is 6% less compared to their WT mice (Flurkey, Papaconstantinou et al. 2002).

Snell dwarves' protection from oxidative stress is two-fold. First, they have an altered response to oxidative stress with reduced MEK-ERK cascade activation and a lack of

phosphorylation of c-Jun at Ser63 as well as heightened catalase response to hydrogen peroxide. Second, Snell dwarves have enhanced base excision repair activity (Madsen, Hsieh et al. 2004, Page, Salmon et al. 2009). Fibroblast cells from Snell dwarf mice also have reduced generation of ROS, improved antioxidant defenses, increased resistance to oxidative stress, and reduced oxidative damage (Murakami, Salmon et al. 2003, Bartke and Brown-Borg 2004, Salmon, Murakami et al. 2005, Maynard and Miller 2006). Snell Dwarf mice are protected against diabetes and cancer, with reduced bodyweight in the adults compared to WT mice, and with elevated β3-adrenergic signaling (Bielschowsky and Bielschowsky 1959, Flurkey, Papaconstantinou et al. 2002, Boylston, Gerstner et al. 2004, Alderman, Flurkey et al. 2009, Bartke and Westbrook 2012, Cannavo and Koch 2017, Simona Negreş, Cornel Chiriţă et al. 2017). β3-adrenergic agonist drugs have been suggested for treatment of diabetes and heart failure, and in contrast to β1-adrenergic signaling, β3-adrenergic stimulation reduces myocardial contractility and myocardial oxygen consumption (Gauthier, Tavernier et al. 1996, Kitamura, Onishi et al. 2000, Varghese, Harrison et al. 2000, Cheng, Zhang et al. 2001, Masutani, Cheng et al. 2013, Belge, Hammond et al. 2014, Balligand 2016), salutary features for longevity. Exercise capacity and cardioprotection have not been examined in this model.

Adenylyl Cyclase Type 5 (AC5) KO Mice (Median Age of Survival of AC5 KO is Increased by 32% Compared to WT With Median Age of Survival of 25 Months): AC5 is one of 10 AC isoforms, which are key to sympathetic regulation and cyclic AMP (cAMP) generation (Vatner, Pachon et al. 2015). AC5 KO mice extend lifespan by 32% compared to WT with no gender differences (Yan, Vatner et al. 2007). AC5 KO mice are protected against oxidative stress via the Sirtuin (SIRT) 1 /FoxO3a and the MEK/ERK pathways (Yan, Vatner et al. 2007, Lai, Yan et al. 2013) (Figure 2). AC5 KO mice, with their decreased β-adrenergic signaling, exhibit enhanced exercise capacity in both young and old animals, are protected against obesity and diabetes when challenged with high fat diet against osteoporosis, cancer, aging-induced cardiomyopathy, and heart failure induced by pressure overload or chronic catecholamine cardiomyopathy (Okumura, Takagi et al. 2003, Yan, Vatner et al. 2007, Lai, Yan et al. 2013, De Lorenzo, Chen et al. 2014, Ho, Zhao et al. 2015, Vatner, Yan et al. 2015, Bravo, Vatner et al. 2016). It is important to note that the protective features of decreased β-adrenergic signaling, primarily refer to β1 and β2-adrenergic signaling, which are the major β-adrenergic subtypes responsible for its adverse effects which include tachycardia, increased myocardial contractility and increased myocardial oxygen consumption, all of which act to intensify the adverse effects of heart failure and myocardial ischemia. AC5 KO mice also share organ specific mechanisms in the liver, heart, brain and skeletal muscle via genes and pathways common to the healthful aging model of calorie restriction (Yan, Park et al. 2012). This is particularly related to the metabolic phenotype, which suggests a unified theory for longevity and stress resistance. A pharmacological inhibitor of AC5 also exhibits protection against myocardial ischemia-reperfusion injury (Zhang, Levy et al. 2018).

Growth Hormone Receptor (GHR) KO Mice (Median Age of Survival, of GHR KO is: Increased by 31% Compared to WT Median Age of Survival of 27 Months): GHR is known for regulation of growth and other biological functions including metabolism and

control of physiological processes related to the cardiovascular, renal, and reproductive systems (Dehkhoda, Lee et al. 2018). GHR KO mice exhibit an increased lifespan in both male and female by 40% and 21% respectively, Ola-BALB/cJ background mice (Coschigano, Holland et al. 2003). However, when the GHR gene is disrupted at 6 weeks of age, GHR KO female mice, but not male mice, exhibit increased lifespan (Junnila, Duran-Ortiz et al. 2016). Calorie restriction (Bonkowski, Dominici et al. 2009) and intermittent fasting (Arum, Bonkowski et al. 2009) failed to extend lifespan further in GHR KO mice. Under hyperthermic conditions, female GHR KO mice exhibit a 14% increase in lifespan compared to when they are housed at room temperature, while male GHR KO mice do not exhibit increased lifespan in the hyperthermic environment. (Fang, McFadden et al. 2020). The further increase in lifespan in female GHR KO mice under hyperthermic conditions, may relate to improved insulin sensitivity when compared to male GHR KO mice (Fang, McFadden et al. 2020), though the mechanisms behind the gender differences in GHR KO mice need further study. The mechanism mediating longevity in GHR KO mice is complex, but involves upregulation of free-radical scavengers, increased insulin sensitivity, and activation of mitochondrial biogenesis through increased levels of AMPK, sirtuins, and PGC1α levels (Basu, Qian et al. 2018). In GHR KO mice, SOD2 and FoxO1 levels are also upregulated and p38 MAPK is activated (Al-Regaiey, Masternak et al. 2005). These mechanisms lead to protection against a variety of age-related diseases. GHR KO mice exhibit protection against diabetes, with increased insulin sensitivity and glucose tolerance, but do not show protection against obesity (List, Sackmann-Sala et al. 2011). GHR KO mice also show protection against a variety of neoplasms (Ikeno, Hubbard et al. 2009), hypertension and cardiomegaly (Egecioglu, Andersson et al. 2007). The effects of GHR KO on exercise performance and β-adrenergic signaling have yet to be examined.

p66 SHC-Transforming Protein 1 (p66shc) KO Mice (Male Median Age of Survival, of p66 shc KO is Increased by 30% Compared to WT Median Age of Survival of 26 Months): p66 SHC is a protein isoform of the SHC1 gene located on chromosome 1 and has been shown to be involved in maintaining the redox balance (Nemoto and Finkel 2002, Giorgio, Berry et al. 2012) which makes it an important regulator of oxidative stress, apoptosis, and cellular proliferation (Galimov 2010). P66shc is an adapter protein, which induces the production of ROS through direct upregulation of NADPH oxidase and inhibition of antioxidant enzymes (Galimov 2010). This leads to ROS as secondary messengers resulting in apoptosis of cells. Deletion of the p66 SHC gene (p66shc KO) eliminates these features, decreases oxidative stress (Napoli, Martin-Padura et al. 2003, Menini, Amadio et al. 2006, Carpi, Menabo et al. 2009) with activation of NF-κB signaling (Menini, Amadio et al. 2006) and increases lifespan in male mice by up to 30% when compared to WT in normal housing environments (Migliaccio, Giorgio et al. 1999). Lifespan was not investigated in female mice in this model. Interestingly, when studied under natural conditions, i.e. non-laboratory conditions, low temperature, and reduced food availability, p66shc KO mice exhibited shorter survival (Giorgio, Berry et al. 2012). This is most likely due to the function of p66shc as important adaptor protein to increased environmental stress and its absence can be detrimental in situations of environmental stress, e.g., extreme temperatures and lack of food. Therefore, deletion of p66shc proves to be an

effective model in extending lifespan under conditions of ambient temperature, lack of predators, and excessive food availability.

Furthermore, p66shc KO mice also reduce the onset of age-related diseases including diabetic glomerulopathy (Menini, Amadio et al. 2006), cardiac stress (Carpi, Menabo et al. 2009), and vascular disease (Napoli, Martin-Padura et al. 2003). Additionally, p66shc deletion has been shown to be associated with decreases in proliferation of ovarian, breast, and prostate cancer (Veeramani, Igawa et al. 2005, Bhat, Baba et al. 2014, Muniyan, Chou et al. 2015). In terms of obesity, the protection of p66shc KO mice is not as clear. While these mice exhibit a decreased body mass (Berniakovich, Trinei et al. 2008, Ciciliot, Albiero et al. 2015), they do not exhibit the improved glucose tolerance and insulin sensitivity that would be expected (Ciciliot, Albiero et al. 2015). Similar results were found in humans, such that patients with low levels of p66shc were leaner, but were not protected from diabetes (Ciciliot, Albiero et al. 2015). Exercise capacity is also complex. On a normal diet no difference in exercise capacity was noted between p66shc KO mice and their WT, but on a high fat diet the p66shc KO mice maintain their exercise capacity, whereas WT on a high fat diet gain weight and exhibit reduced exercise capacity with greater ROS production (Granatiero, Gherardi et al. 2017), suggesting p66shc KO mice can tolerate the increased ROS associated with high-fat diets. β-adrenergic signaling has not been examined.

Angiotensin II Receptor Type 1a (Agtr1a) KO Mice (Male Median Age of Survival, of Agtr1a KO is Increased by 26% Compared to WT with Median Age of Survival of 26 Months): Angiotensin II receptor Type 1 is a central component of the renin-angiotensin system and mediates the biological actions of angiotensin II (Guo, Sun et al. 2001). Lack of Agtr1a extends lifespan by 26% in male mice, reduces oxidative damage and prevents age-induced mitochondrial loss with upregulated expression of the pro-survival genes nicotinamide phosphoribosyl transferase and SIRT3 (Benigni, Corna et al. 2009). There are no data available on lifespan in female Agtr1a KO mice. This reduction in oxidative stress is mediated by a reduction in Ang-II-dependent upregulation of p47phox which functions to activate NAD(P)H oxidase, resulting in increased endothelial O_2^- production (Nickenig and Harrison 2002, Hirono, Yoshimoto et al. 2007).

Cardioprotection in Agtr1a KO is controversial (Zhu, Zhu et al. 2003). The salutary effects include permanent coronary artery occlusion (CAO) which caused 13.6% of WT mice deaths in the first week post-op in contrast with 5.9% of deaths in Agtr1a KO mice. More impressive is that no KO mice died in the following three weeks, during which period 9.1% of WT mice died (Harada, Sugaya et al. 1999). However, another study of male and female Agtr1a KO mice with 6-week CAO showed that there was no difference in survival between WT and Agtr1a KO mice, and myocardial infarct size among WT males, WT females, KO males and KO females (Bridgman, Aronovitz et al. 2005). Although both males and females were studied, the data were not separated by gender. In that study, the extent of hypertrophy, reflected by left ventricular weight to body weight (LV/BW) and myocyte cross sectional area following permanent CAO were also examined. LV/BW and myocyte cross-sectional area did not change in female Agtr1a KO after permanent CAO compared to the sham group, but all male and female WT mice and male Agtr1a KO mice developed approximately a 50% increase in LV/BW and myocyte cross-sectional area following CAO,

compared to sham. The mechanism mediating these gender differences was not discussed (Bridgman, Aronovitz et al. 2005).

With high fat diet, both WT and Agtr1a KO mice gain body weight similarly, but Agtr1a KO mice exhibited lower body fat (Ma, Corsa et al. 2011). Obesity-related kidney injury was observed in the Agtr1a KO mice, which was ascribed to an increase in Agtr1b expression, suggesting a role for the broader Angiotensin II type 1 receptor (Ma, Corsa et al. 2011). Agtr1a KO mice also developed significant systolic and diastolic dysfunction with streptozotocin induced diabetes (Yong, Thomas et al. 2013). In terms of cancer, endothelium-specific Agtr1a KO mice have been shown to be protected from metastasis of melanoma to the lungs (Ishikane, Hosoda et al. 2018).

The studies on overexpression of Agtr1a in mice have shown deleterious effects such as increased hypertrophy, interstitial fibrosis (Paradis, Dali-Youcef et al. 2000), and arrhythmogenicity (Rivard, Paradis et al. 2008). Exercise performance and the role of β-adrenergic signaling have not been examined in this model.

Regulator of G Protein Signaling 14 (RGS14) KO Mice (Median Age of Survival, of RGS14 KO is Increased by 26% Compared to WT Median Age of Survival of 23 Months): RGS14 is a complex RGS family member that contains a canonical RGS domain and a tandem (R1 and R2) Ras/Rap binding domain. The RGS14 KO mice have enhanced brown adipose tissue with improved metabolism (Vatner, Zhang et al. 2018). RGS14 KO extended the median lifespan by 17% in males and 29% in females. RGS14 KO mice are protected against oxidative stress, obesity, diabetes, cancer, exercise intolerance and cardiac stress with decreased β-adrenergic signaling (Zhang, Vatner et al. 2016, 134:A18750, Guers, Oydanich et al. 2017, 136:A18790, Oydanich, Zhang et al. 2018, Vatner, Zhang et al. 2018).

Insulin-like Growth Factor (IGF) Type 1 Receptor (1R) Heterozygote Mice (Median Age of Survival, of IGF-1R $^{+/-}$is Increased by 24% Compared to WT Median Age of Survival of 21 Months): IGF-1R is one of the two IGF cell surface receptors. IGF-1R regulates the effects of IGF-1, and its signaling involves auto-phosphorylation and subsequent tyrosine phosphorylation of the insulin receptor substrate and Shc (Shc represents Src homology/collagen proteins, which are encoded by the SHC1 gene) which is also important in the p66Shc KO model of longevity (Delafontaine, Song et al. 2004). Increased longevity is sex-specific, with females having 33% and males having 15.9% longer lifespans than controls with a 129/J background (Holzenberger, Dupont et al. 2003). In another lifespan study by the same group using mice with a C57BL/6J background, although females still live 11% longer than controls, males have a maximum lifespan reduced by 13% (Xu, Gontier et al. 2014). This discrepancy is explained by the different background strains in the longevity phenotypes, e.g., the IGF1 levels, which correlate inversely with longevity. The C57BL/6J WT have lower levels of IGF and live longer than 129/J WT (Yuan, Tsaih et al. 2009, Xu, Gontier et al. 2014).

The differences on lifespan between males and females may relate to the fact that female IGF-1R$^{+/-}$ mice are more resistant to oxidative stress with higher survival compared to their WT littermates when challenged with paraquat, whereas this improved resistance to

oxidative stress was not found in male IGF-1R$^{+/-}$ mice (Holzenberger, Dupont et al. 2003, Bokov, Garg et al. 2011). The protection observed in the heterozygote mice is mediated by activation of the MAPK pathway along with a reduction in p66Shc and ERK1/2 phosphorylation, and alanine-leucine transaminase levels (Holzenberger, Dupont et al. 2003, Bokov, Garg et al. 2011). *In vitro*, myoblasts from IGF-1R$^{+/-}$ mice are resistant to oxidative stress induced by H_2O_2 and UV light (Thakur, Garg et al. 2013). Both aged male and female IGF-1R$^{+/-}$ mice exhibit insulin resistance (Holzenberger, Dupont et al. 2003), and male, but not female, IGF-1R$^{+/-}$ mice also display glucose intolerance (Holzenberger, Dupont et al. 2003, Bokov, Garg et al. 2011). With high fat diet, both male and female IGF-1R$^{+/-}$ mice develop insulin resistance and impaired glucose tolerance (Garg, Thakur et al. 2011). Both adult male and female IGF-1R$^{+/-}$ mice display a lower body weight than WT mice, however, when challenged with a high fat diet, female IGF-1R$^{+/-}$ mice have greater body weight than female WT but male IGF-1R$^{+/-}$ mice have lower body weight than male WT mice (Garg, Thakur et al. 2011).

This model also protects against cancer. One study showed that heterozygotes are protected from colitis and tumorigenesis, due to reduced oxidative damage and accordingly, prevention of TNF-α, IL-6, NF-κB and STAT3 cascade activation in colonic epithelial cells (Wang, Yang et al. 2019). IGF-1R antibodies are also used clinically in treating cancer (Beltran, Mitchell et al. 2009, Tolcher, Sarantopoulos et al. 2009, Tap, Demetri et al. 2012). However, the lower number of fatalities in IGF-1R$^{+/-}$ males and females did not attain statistical significance (Bokov, Garg et al. 2011).

Exercise capacity, cardioprotection, and the role of β-adrenergic signaling have not been examined in this model.

Klotho Overexpressed Mice (Median Age of Survival, of Klotho Overexpressed is: Increased by 22% Compared to WT Median Age of Survival of 32 Months): The Klotho proteins, α-Klotho, β-Klotho, and γ-Klotho, are important transmembrane proteins involved in aging (Kuro-o, Matsumura et al. 1997). Klotho overexpression has been shown to increase lifespan in both male and female mice similarly (Kurosu, Yamamoto et al. 2005). There are two Klotho overexpressed mice lines that were studied, EFmKL46 or EFmKL48. In EFmKL46 mice, lifespan is extended in males by 20% and in females by 18.8%. In EFmKL48, mice lifespan is extended in males by 30.8% and in females by 19% (Kurosu, Yamamoto et al. 2005). Higher levels of Klotho correlate with higher levels of the p53 gene as well as antioxidant enzymes including catalase, SOD, peroxiredoxin, and glutathione peroxidase (Kimura, Shiizaki et al. 2018).

However, Klotho, seems to have differing results in protection against age-related diseases. Klotho overexpression protects against diet-induced obesity (38), but not diabetes (Samms, Cheng et al. 2016). In terms of cardioprotection, Klotho KO mice develop exaggerated cardiac hypertrophy in response to chronic isoproterenol administration, consistent with the protection observed in the Klotho overexpressed mice (Xie, Cha et al. 2012). Klotho is also upregulated in human hearts with cardiomyopathy compared to its level in normal human hearts, but it is not known if this is a cause of or a response to the cardiomyopathy (Poelzl,

Ghadge et al. 2018). Another clinical study revealed higher Klotho levels associated with the absence of atrial fibrillation in hemodialysis patients (Nowak, Friedrich et al. 2014).

In terms of cancer, Klotho overexpression acts as a tumor suppressor, e.g. it decreases tumor growth in diffuse large B-cell lymphoma (Zhou, Fang et al. 2017) and suppresses growth and pulmonary metastasis of osteosarcoma (Li, Xiao et al. 2020). Furthermore, while there have been studies showing Klotho is increased after exercise training in Sprague Dawley rats compared to their control group (Ji, Luan et al. 2018) and in humans compared to their baseline level before exercise training (Tan, Chu et al. 2018), there haven't been any studies showing that increases in Klotho directly lead to improvement in exercise performance. Therefore, its role in mediating exercise capacity requires further study. The role of β-adrenergic signaling has also not been examined in this model.

Mitochondrial Targeted Catalase (MCAT) Overexpressed Mice (Median Age of Survival, of MCAT Overexpressed is increased by 19% Compared to WT with Median Age of Survival of 25 Months): Catalase (CAT) is a ubiquitously expressed antioxidant enzyme primarily located in peroxisomes, that catalyzes the decomposition of H_2O_2 to O_2 and H_2O (Halliwell and Gutteridge 1989). Catalase has a central role in regulating the cellular level of H_2O_2, and this catabolic action protects cells from oxidative stress (Gaetani, Ferraris et al. 1996, Nandi, Yan et al. 2019). Lifespan of MCAT overexpressed mice is increased similarly in males and females (Schriner, Linford et al. 2005).

In MCAT overexpressed mice, oxidative damage, H_2O_2 production and H_2O_2-induced aconitase inactivation are attenuated. Furthermore, the development of mitochondrial deletions is reduced in this murine model (Schriner, Linford et al. 2005, Dai, Santana et al. 2009). MCAT overexpressed mice are also protected from age-associated decline in AMP-activated protein kinase (AMPK) activity and mitochondrial density (Lee, Choi et al. 2010), resulting in reduced DNA oxidation in all the tissues compared to control mice (Perez, Bokov et al. 2009). CAT overexpressed-derived embryonic fibroblasts are resistant to H_2O_2 toxicity, demonstrating increased catalase-specific activity (Mele, Van Remmen et al. 2006). Aged MCAT overexpressed mice exhibit improved exercise performance with enhanced mitochondrial antioxidant activity and improved muscle function (Umanskaya, Santulli et al. 2014). MCAT overexpressed mice are also protected against lipid induced insulin resistance in muscle and demonstrate better muscle mitochondrial function (Lee, Choi et al. 2010). Body weights and body fat composition were similar in WT and MCAT overexpressed mice (Lee, Choi et al. 2010). MMTV-PyMT, (mouse mammary tumor virus-polyoma middle tumor-antigen) is a mouse breast cancer model. When MMTV-PyMT mice are crossed with MCAT overexpressed mice, they exhibit lower incidence of tumor invasiveness than PyMT breast cancer mice without MCAT overexpression (Goh, Enns et al. 2011).

Ang II-induced heart failure and the cardiovascular consequences of aging, e.g. increased LV mass, decreased diastolic function and myocardial performance, are attenuated in MCAT overexpressed mice with reduced oxidative stress and enhanced mitochondrial function (Dai, Santana et al. 2009, Dai, Johnson et al. 2011). MCAT overexpressed mice also exhibit decreased β-adrenergic signaling which protects against cardiac remolding (Uribe and Andersson 2019).

Ribosomal Protein S6 Kinase β−1 (S6K1) KO Mice (Median Age of Survival, of S6K1 KO is Increased by 19% in Females Compared to WT Median Age of Survival of 28 Months): S6K1 is the principal kinase effector downstream of mammalian target of rapamycin complex 1 (mTORC1), which lowers mitochondrial ROS levels (Binsch, Jelenik et al. 2017). Longevity as measured by median lifespan was enhanced in female S6K1 KO mice by 19%, but no such difference was observed in males (Selman, Tullet et al. 2009). These gender differences could be due to estrogen regulation of S6K1 activation (Jaffer, Shynlova et al. 2009). Young male S6K1 KO mice, due to a marked increase in metabolic rate and lipolysis, exhibit lower body weight and have improved glucose tolerance and insulin sensitivity compared to WT in response to either normal diet (Um, Frigerio et al. 2004) or high fat diet (Um, Frigerio et al. 2004, Binsch, Jelenik et al. 2017). In addition, improved glucose tolerance and insulin sensitivity were also observed in 20 month old female S6K1 KO compared to WT mice in response to high fat diet, though this protective feature was not observed in young female S6K1 KO mice (Selman, Tullet et al. 2009).

S6K1 KO with high fat diet also exhibited greater running distance, longer running times, and reduced triglyceride contents in liver and skeletal muscle after 4 weeks of exercise training compared to WT mice (Binsch, Jelenik et al. 2017).

Two mechanisms mediate increased oxidative stress by S6K1: 1) mitochondrial superoxide production is directly increased, and 2) S6K1 activation mediates uncoupling of eNOS, decreasing antioxidant capacity (Rajapakse, Yepuri et al. 2011). In addition, S6K1 KO mice exhibit less mitochondrial ROS production (Binsch, Jelenik et al. 2017). *In vitro*, overexpression of S6K1 results in increased superoxide and decreased NO production (Rajapakse, Yepuri et al. 2011).

S6K1 levels are elevated in breast cancer, a result that is mediated by estrogen receptors, whereas S6K1 also regulates ligand independent estrogen receptor activity. Together the two form a feed-forward loop, promoting breast cancer cell proliferation (Maruani, Spiegel et al. 2012). In addition, S6K1 inhibitors induce autophagy and apoptosis in cervical cancer cells (Nam, Yi et al. 2019) and BT474 breast cancer cells (Park, Jin et al. 2015) *in vitro*. Cardioprotection, and the role of β-adrenergic signaling have not been examined in this model.

(2) A Longevity Model Not Protected Against Oxidative Stress:

Growth Hormone Receptor/Binding Protein (GHR/BP) KO Mice (Median Age of Survival, of GHR/BP is Increased by 47% Compared to WT Median Age of Survival of 23 Months): GHR/BP KO mice have a longer lifespan in both males by 55% and females by 38% (Coschigano, Clemmons et al. 2000). Growth hormone binding protein (GHBP), is a truncated form of the GHR, which modulates growth hormone action (Baumann 2002). GHR regulates growth and other biological functions including metabolism and controlling physiological processes related to the cardiovascular, renal, and reproductive systems (Dehkhoda, Lee et al. 2018). GHR/BP KO mice with disrupted GHR and GHBP, exhibit severe postnatal growth impairment, proportionate dwarfism, decreased levels of IGF1 and increased GH levels (Zhou, Xu et al. 1997).

GHR/BP KO mice do not confer longevity by improved free-radical scavenging in the liver and kidney. In the kidney SOD1 is lower and Gpx is higher in GHR/BP KO mice. Lipid peroxidation is higher only in female GHR/BP KO mice. GHR/BP KO males are more susceptible to paraquat toxicity compared to females or normal males (Hauck, Aaron et al. 2002). GHR/BP KO are protected against cancer, with a lower percentage of tumor-bearing mice compared to WT and live longer than WT even when tumors are present. GHR/BP KO are also less susceptible to metastasis (Ikeno, Hubbard et al. 2009). GHR/BP KO mice have improved grip strength, balance, and motor coordination in middle and old age in both males and females (Arum, Rickman et al. 2014). Although GHR/BP KO mice exhibit smaller body size and lower body weight than WT, there are no studies on protection against obesity when challenged with high fat diet. Protection from diabetes, cardioprotection, and the role of β-adrenergic signaling have also not been examined in this model.

(3) Longevity Models With Oxidative Stress Protection Data Controversial:

Ames Dwarf Mice (Median Age of Survival, of Ames Dwarf is Increased by 57% Compared to WT Median Age of Survival of 21 Months): Ames Dwarf mice are characterized as having deficiencies in hormones of the anterior pituitary, most notably growth hormone, prolactin, and thyroid-stimulating hormone (Bartke and Brown-Borg 2004), which is similar to the Snell Dwarf mice and GHR KO mice (Bartke and Brown-Borg 2004, Rohrbach, Teichert et al. 2008). These mice also have an extended lifespan by 64% in males and 49% in females (Brown-Borg, Borg et al. 1996). The mechanism for the shorter median lifespan of WT mice was not discussed. These mice show resistance to oxidative stress induced by paraquat and diquat, both of which are known producers of reactive oxygen species (Bokov, Lindsey et al. 2009). These mice also have elevated levels of catalase and SOD1 in the hypothalamus (Hauck and Bartke 2000). However, another study showed the opposite, with increased vascular oxidative stress with decreased expression of SOD and Gpx in the aortas of Ames dwarf mice (Csiszar, Labinskyy et al. 2008). Ames dwarf mice show protection against diabetic risk factors, cancer, and dobutamine-induced cardiac stress (Dominici, Hauck et al. 2002, Ikeno, Bronson et al. 2003, Bokov, Lindsey et al. 2009). While there are no studies on exercise performance, Ames dwarf mice do show increased antioxidant defense in skeletal muscle following acute and chronic exercise (Romanick, Rakoczy et al. 2004). The role of β-adrenergic signaling in this model has not been examined.

Mitochondrial 5-Demethoxyubiquinone Hydroxylase (MCLK1) Heterozygote Mice (Median Age of Survival, of MCLK1+/− is Increased by 31% Compared to WT Median Age of Survival of 22 Months): MCLK1 heterozygous mice exhibit enhanced longevity in both male and female mice (Liu, Jiang et al. 2005). On average, both sexes live 31% longer than WT. The cause of the short median lifespan in WT mice was not discussed. As previously mentioned, this may be due to the different background of WT mice and housing conditions. Inactivation of MCLK1 in embryonic stem cells has been shown to incur protection from oxidative stress and damage to DNA (Liu, Jiang et al. 2005). However, in the MCLK1 +/− mouse model, a different, more complex result was discovered. These mice have increased production of ROS and decreased antioxidant production resulting in increased mitochondrial oxidative stress and mitochondrial dysfunction, but have decreases

in cytosolic oxidative damage and low non-mitochondrial oxidative damage with reduced systemic oxidative stress markers associated with aging (Lapointe and Hekimi 2008). A mechanism proposed for these differences involves a reduction in the rate of cytoplasmic ROS producing processes due to the decreased levels of ATP and total NAD (Lapointe and Hekimi 2008). This model shares some congruence with the theory of mitochondrial hormesis, suggesting that early increases in oxidative stressors can lead to adaptive responses that promote longevity. This mechanism also promotes protection against cancer in this model, via an increase in tumor latency (Wang, Wang et al. 2012). Further studies on protection against diabetes, obesity, cardiac stress, exercise intolerance, and the role of β-adrenergic signaling have yet to be conducted.

Insulin Receptor Substrate 1 (IRS1) KO Mice: (Median Age of Survival, of IRS1 KO is Increased by 18% Compared to WT Median Age of Survival of 24 Months): IRS1 protein is one of the primary mediators of insulin-dependent mitogenesis and regulation of glucose metabolism in most cell types involving PI3K/Akt and ERK/MAP kinase pathways (White 2002, Mardilovich, Pankratz et al. 2009). It has been shown to increase longevity in IRS1 KO male by 15% and female mice by 21% (Selman, Partridge et al. 2011). The role of IRS1 in regulating oxidative stress is controversial. Overexpression of IRS1 has been shown to reduce oxidative stress and prevent autophagy (Chan, Kikkawa et al. 2012). However, IRS1 KO mice maintain normal catalase levels with aging leading to better oxidative stress defense, while WT mice exhibit decreases in catalase levels (Selman, Lingard et al. 2008). IRS1 KO mice are protected against obesity with less body weight and fat mass during aging (Selman, Lingard et al. 2008), but not against diabetes with impaired glucose tolerance, insulin sensitivity (Araki, Lipes et al. 1994, Selman, Lingard et al. 2008) and cardiac stress (Furumoto, Fujii et al. 2005). The findings on cancer protection are controversial. IRS1 KO (Ma, Gibson et al. 2006) and IRS1 overexpressed (Dearth, Cui et al. 2006) mice both exhibit increases in mammary tumor metastasis making the role of IRS1 in cancer difficult to interpret. No studies have examined either the KO or overexpressed models in terms of β-adrenergic signaling.

(4) Longevity Models With Oxidative Stress Not Studied:

Cytosolic Form of Phosphoenolpyruvate Carboxykinase (PEPCK-C) Overexpressed Mice (Median Age of Survival, unspecified): PEPCK-C is present in the liver, kidney cortex and brown and white adipose tissue; and is involved in gluconeogenesis and/or glyceroneogenesis (Croniger, Olswang et al. 2002). Both male and female PEPCK-C overexpressed mice are still able to reproduce after the age of 21 months (Hakimi, Yang et al. 2007). PEPCK-C overexpressed mice have enhanced exercise capacity and are able to maintain respiratory exchange ratios below unity over 40 minutes of strenuous exercise. Conversely, WT mice exceed RER unity after less than 10 minutes. Performance was improved even in old animals compared to young WT. Lactate levels in PEPCK-C overexpressed mice were reduced during exercise compared to baseline whereas WT had a 4-fold increase in lactate in response to exercise (Hakimi, Yang et al. 2007). PEPCK-C overexpressed mice have lower body weight despite a 60% increase in food intake, lower percentage of adipose tissue even when aged, but greater blood glucose levels compared to WT mice (Hakimi, Yang et al. 2007). Many of these attributes result in longevity, but the

median age of survival of PEPCK-C overexpressed mice was not reported, Cancer, cardioprotection, β-adrenergic signaling and oxidative stress have not been examined in this model.

Pregnancy-Associated Plasma Protein-A (PAPPA) KO Mice (Median Age of Survival, of PAPPA KO is increased by 26% Compared to WT Median Age of Survival of 21 Months): PAPPA is the largest of the pregnancy associated proteins, produced by both the embryo and the placenta during pregnancy. This protein has several different functions, including preventing recognition of the fetus by the maternal immune system, matrix mineralization and angiogenesis (Fialova and Malbohan 2002). PAPPA-KO increases longevity to a similar extent in females and in males (Conover, Bale et al. 2010). The median lifespan of the WT was only 21 months. The cause of the short median lifespan of WT mice was not discussed. PAPPA KO mice are protected against cancer with a reduction in neoplasms observed at necropsy compared to wild-type (Conover and Bale 2007). Reducing PAPPA protein expression decreases tumor growth in-vivo whereas overexpression and secretion PAPPA protein in the xenograft cell-line resulted in augmented tumor growth via upregulation of the IGF pathway. Accordingly, the over-expression of PAPPA alone did not result in augmented growth of the tumor cell line. Only when PAPPA protein secretion was also upregulated did the proliferative phenotype become apparent (Pan, Hanada et al. 2012). Spontaneous pathology of the heart discovered at necropsy was absent in aged KO mice, whereas 50% of WT mice had evidence of disease (Conover and Bale 2007). Female KO mice were more tolerant of glucose challenge and had increased insulin sensitivity with high fat and high sucrose diet (Hill, Arum et al. 2015). PAPPA KO mice exhibit partial protection from obesity with a reduction in visceral fat depot weight and an increase in circulating adiponectin but no difference in percent-body-fat compared to WT (Conover and Bale 2007, Heitzeneder, Sotillo et al. 2019). There are no studies on exercise capacity, cardioprotection, β-adrenergic signaling and oxidative stress.

V. *Caenorhabditis elegans (C. elegans)* Models of Longevity Associated with Oxidative Stress Protection

In *C. elegans*, as with other models, the accumulation of oxidative damage is deleterious to both the lifespan and health span of the animal. Several mutant models of protection from oxidative stress in *C. elegans* are long-lived compared to their wild type counterparts (Friedman and Johnson 1988, Friedman and Johnson 1988, Kenyon, Chang et al. 1993, Li, Gao et al. 2007, Mehta, Steinkraus et al. 2009). Mutations in AGE-1, daf2, RLE-1, VHL-1, and HIF-1 all yielded longer lives and are resistant to oxidative stress (Friedman and Johnson 1988, Friedman and Johnson 1988, Kenyon, Chang et al. 1993, Li, Gao et al. 2007, Mehta, Steinkraus et al. 2009). In addition, several other *C. elegans* models would have been expected to have deleterious effects from their oxidative stress response, based on data from mouse models, but did not demonstrate significant improvement in longevity from these *C. elegans* models (Oh, Mukhopadhyay et al. 2005, Lehtinen, Yuan et al. 2006, Leiser, Begun et al. 2011). For example, JNK1 activation by oxidative stress in mice results in a pro-inflammatory phenotype in the kidney (Wu, Mei et al. 2009) and lack of JNK1 in mouse embryonic fibroblasts results in increased sensitivity to oxidative stress (Ventura, Cogswell

et al. 2004). However, overexpression of JNK1 in *C. elegans* yields a significant extension in life-span (Oh, Mukhopadhyay et al. 2005). Similarly, MST-1 overexpression in the hearts of mice resulted in a fibrotic phenotype, which suggests that MST-1 can mediate oxidative stress induced damage to the heart (Yamamoto, Yang et al. 2003). In contrast, overexpression of the CST-1, the MST-1 orthologue in *C. elegans*, resulted in longer lifespan (Lehtinen, Yuan et al. 2006). Finally HIF-1a protects against oxidative stress in mice (Li, Zhou et al. 2019), but the HIF-1 KO in *C. elegans* resulted in enhanced lifespan (Leiser, Begun et al. 2011). In each of these models, protection was conferred via indirect activation of daf-16, which both alone and as part of a complex of proteins, is protective against oxidative stress (Oh, Mukhopadhyay et al. 2005, Lehtinen, Yuan et al. 2006, Leiser, Begun et al. 2011, Lin, Sen et al. 2018). Changes in environmental conditions, particularly temperature, often affected the lifespan in these models, sometimes eliminating it entirely (Van Voorhies and Ward 1999, Xiao, Zhang et al. 2013). Additional studies on *C. elegans*, where oxidative stress is increased, are discussed in the mitochondrial hormesis section, which follows the Section VII.

VI. Non-Human Primate Models of Longevity Associated with Oxidative Stress Protection

Among the non-human primate studies on calorie restriction and lifespan, only those studies carried out at the Wisconsin National Primate Research Center in Rhesus monkeys showed an increase in lifespan, as well as age-related diseases (Colman, Anderson et al. 2009, Colman, Beasley et al. 2014). In contrast, the National Institute on Aging study on lifespan, also in Rhesus monkeys, did not find an extended lifespan (Mattison, Roth et al. 2012). However, both studies reported beneficial effects of caloric restriction on age-related diseases (Colman, Anderson et al. 2009, Mattison, Roth et al. 2012, Colman, Beasley et al. 2014), with reduced adiposity (Colman, Roecker et al. 1998, Edwards, Rudel et al. 1998), increased insulin sensitivity (Gresl, Colman et al. 2003), and reduced oxidative damage (Zainal, Oberley et al. 2000). The differences of lifespan in the two studies in response to calorie restriction have been attributed to study design, husbandry and diet composition (Mattison, Colman et al. 2017). However, we also think that lifespan studies in primates in captivity may be complicated by many factors not observed when the primates are in their natural environment.

VII. Human Models of Longevity Associated with Oxidative Stress Protection

While there are immense challenges to mounting a randomized controlled study on the effects of calorie restriction on human lifespan, existing studies do suggest that calorie restriction enhances human longevity (Trepanowski, Canale et al. 2011, Ravussin, Redman et al. 2015, Redman, Smith et al. 2018). This is due, in large part, to the reduction in caloric intake, which protects against obesity and subsequently a decrease in obesity-associated morbidity and mortality. Calorie restriction also protects against other diseases and pathologic processes of aging that increase morbidity and mortality, e.g., cardiovascular diseases (Meyer, Kovacs et al. 2006, Hammer, Snel et al. 2008, Riordan, Weiss et al. 2008),

diabetes and metabolic diseases (Larson-Meyer, Heilbronn et al. 2006, Weiss, Racette et al. 2006, Ryan, Ortmeyer et al. 2012), inflammation (Imayama, Ulrich et al. 2012) and cancer (Wei, Brandhorst et al. 2017, Lope, Martín et al. 2019, de Groot, Lugtenberg et al. 2020).

Calorie restriction reduces ROS production in healthy people (Redman, Smith et al. 2018). Even in those that are already obese, calorie restriction is linked to a reduction in oxidative stress markers (Buchowski, Hongu et al. 2012). Calorie restriction also slows metabolic rate (Heilbronn, de Jonge et al. 2006, Civitarese, Carling et al. 2007), and lowers oxidative damage (Heilbronn, de Jonge et al. 2006, Buchowski, Hongu et al. 2012, Redman, Smith et al. 2018) in both healthy and overweight individuals.

However, in one of the human studies, resting metabolic rate significantly decreased in the calorie restriction group after 12 months compared to the control group, but no difference was observed at 24 months between the two groups (Ravussin, Redman et al. 2015). Increased mitochondrial biogenesis in healthy humans under calorie restriction is one mechanism to explain the decreased oxidative stress and decreased DNA damage (Civitarese, Carling et al. 2007).

Exercise training also prolongs lifespan, but enhanced exercise performance is not a feature of calorie restriction (Martin, Das et al. 2011, Racette, Rochon et al. 2017). When exercise intolerance occurs in the older population, its severity is augmented by chronic diseases, including heart failure (Del Buono, Arena et al. 2019), diabetes (Poitras, Hudson et al. 2018), lung diseases (Vogiatzis and Zakynthinos 2012) and cancer (Jones, Eves et al. 2009), which all share increased oxidative stress as a mechanism in their pathophysiology. For example, exercise intolerance in patients with heart failure is linked to increased mitochondrial ROS (Shirakawa, Yokota et al. 2019), increased plasma lipid peroxidation (Keith, Geranmayegan et al. 1998, Sawyer 2011), and increased plasma malondialdehyde (Nishiyama, Ikeda et al. 1998) and decreased SOD activity (Nishiyama, Ikeda et al. 1998). However, the relation between exercise and oxidative stress is complex. Acute exercise can actually increase oxidative stress (Fisher-Wellman and Bloomer 2009), whereas long-term exercise training reduces oxidative stress (Liu, Yeo et al. 2000, Elosua, Molina et al. 2003, Vollaard, Shearman et al. 2005) by upregulating antioxidant enzymes such as SOD, Gpx, and glutathione reductase. As noted, exercise also stimulates cellular ROS production in muscle, liver, and other organs; this is due to mitochondrial sources of ROS such as NADPH oxidase or xanthine oxidase and ultimately leads to more efficient mitochondrial ATP production (Coggan, Spina et al. 1990, Lanza, Short et al. 2008, Gomez-Cabrera, Salvador-Pascual et al. 2015, Bouzid, Filaire et al. 2018). The effects of antioxidant supplementation on mitochondrial biogenesis in skeletal muscle are controversial, suggesting that antioxidant supplementation either has little effect or is deleterious to the beneficial adaptations to exercise training in skeletal muscle, highlighting the important role of ROS as second messengers (Gomez-Cabrera, Salvador-Pascual et al. 2015). This role for ROS is supported by the observation that the geographic distribution in the prevalence of glucose-6-phosphate dehydrogenase (G6PD) deficiency correlates with the severity of malaria (Ruwende, Khoo et al. 1995). G6PD deficient red blood cells are unable to provide the optimum red blood cell redox status that is required by malaria parasites for their survival (Vega-Rodriguez, Franke-

Fayard et al. 2009). Lower survival for malaria parasites can explain the lower risk for severe malaria in Africans with G6PD deficiency.

Mitochondrial myopathies serve as a valuable clinical model for the study of oxidative stress. These diseases generally result in increased oxidative stress and higher levels of ROS (Esposito, Melov et al. 1999). Coenzyme Q10 (CoQ10) and its synthetic analogue, idebenone, are examples of antioxidants that have been used successfully to treat patients with mitochondrial myopathies. There is modest evidence to support the rationale of these therapies that scavenging reactive oxygen species can lead to clinical improvement. In a randomized, placebo-controlled, double-blind trial of 85 patients with Leber hereditary optic neuropathy (LHON) (Klopstock, Yu-Wai-Man et al. 2011), idebenone showed a trend for improved vision. Even though the trial demonstrated no benefit from idebenone by intention-to-treat analysis for the primary outcome of visual acuity, these data led to the approval of idebenone in 2015 by the European Medicines Agency for the treatment of visual impairment in adolescent and adult patients with LHON (Erin O'Ferrall 2020). CoQ10 has also been used to treat mitochondrial disorders that lack CoQ10. It should be mentioned that besides its function as an antioxidant, CoQ10 also serves as an integral part of the mitochondrial respiratory function via its role as an electron acceptor. It is not clear which of its two roles, as an antioxidant or mitochondrial electron acceptor, produces a benefit in CoQ10 supplementation for patients with mitochondrial disorders or CoQ10 deficiency. Although not all clinical trials of CoQ10 have been positive (Muller 1990), the consensus is that the treatment is effective with few side effects for patients with mitochondrial disorders including infants and children (Chen, Huang et al. 1997). Some of the controversy related to the role of mitochondria in longevity could be due to a biological phenomenon known as mitochondrial hormesis (Ristow and Zarse 2010), which will be discussed next.

Mitochondrial Hormesis

The controversial relationship between antioxidant supplementation and longevity increases the complexity of understanding the role of ROS in mediating longevity and has led to different theories, such as mitochondrial hormesis. Mitochondrial hormesis refers to conditions whereby increased levels of oxidative stress can lead to healthful aging (Ristow and Zarse 2010). Whereas it is recognized that high levels of oxidative stress are detrimental and lead to increased morbidity and mortality in aging, mitochondrial hormesis, advances the interesting argument that small increases in levels of ROS may not always be detrimental, but rather may function to modulate several signaling pathways, including activation of sirtuins and AMPK, and inhibition of mTOR signaling (Ristow and Schmeisser 2014). All of these pathways have been shown to be involved in extending longevity through increased stress resistance, resulting in a long-term reduction of oxidative stress.

Exercise is a classic example of mitochondrial hormesis (Ristow, Zarse et al. 2009, Hood, Zhang et al. 2018, Musci, Hamilton et al. 2019) which acutely increases ROS production but its chronic influence is to induce healthful aging (Fisher-Wellman and Bloomer 2009, Ristow, Zarse et al. 2009). Such observations of opposing effects under acute and chronic conditions are not an unusually rare phenomenon clinically. For instance, smoking cessation

acutely leads to a more reactive airway and increased secretions and is therefore not recommended for patients undergoing surgery (Bluman, Mosca et al. 1998), whereas chronically the beneficial effects of smoking cessation are enormous. Another example is alcohol exposure which acutely decreases anesthetic requirements, but chronic alcohol consumption, increases anesthetic requirements (Lobo and Lopez 2020) and also has opposing effects on inflammation, with acute exposure reducing inflammation whereas chronic exposure increases inflammation (Mandrekar, Bala et al. 2009). The beneficial effects of regular exercise are partly based on the exercise induced ROS production, which then induce expression of antioxidants, DNA repair and protein degrading enzymes, and result in decreases of oxidative stress (Liu, Yeo et al. 2000, Elosua, Molina et al. 2003, Vollaard, Shearman et al. 2005) and oxidative stress related diseases (Radak, Chung et al. 2005). For example, xanthine oxidase increases ROS, and inhibition of xanthine oxidase impairs gene transcription in response to acute exercise, but does not cause a major effect on long-term exercise training, which induces mitochondrial biogenesis and antioxidant defenses (Wadley, Nicolas et al. 2013). Studies directly linking mitochondrial hormesis and exercise training are still pending (Merry and Ristow 2016).

Calorie restriction is also considered a model of mitochondrial hormesis (Schmeisser, Priebe et al. 2013, Ristow and Schmeisser 2014, Hood, Zhang et al. 2018) by improved mitochondrial function mediated partially through increased mitochondrial turnover. This is based on studies in *C. elegans* (Schmeisser, Priebe et al. 2013) or yeast (Mesquita, Weinberger et al. 2010, Zuin, Carmona et al. 2010) demonstrating extended lifespan conferred by causing mitochondria to emit more reactive oxygen species which, though a defensive response which senses the higher levels, and induces mechanisms to lower oxidative stress (Ristow and Schmeisser 2014). Another example is glucose restriction, which promotes increases in ROS, which induce catalase activity, resulting in increased oxidative stress resistance and in extended lifespan in *C. elegans* (Schulz, Zarse et al. 2007). Finally, extended lifespan with impaired insulin/IGF-1 signaling also involves the mitochondrial hormesis mechanism. Examples include the Ames Dwarf mice, Snell Dwarf mice, GHR KO mice, p66shc KO mice, and IGF-1R$^{+/-}$ mice (Brown-Borg, Borg et al. 1996, Quarrie and Riabowol 2004). Studies in the long-lived *C. elegans* mutant daf-2 model. i.e., the worm orthologue of the insulin/IGF-1 receptor, demonstrate that increased ROS activates the ROS defense enzymes, culminating in reduced ROS levels and extended lifespan (Brys, Castelein et al. 2010, Zarse, Schmeisser et al. 2012). It is important to note that the mechanism of mitochondrial hormesis has not been found in humans or large mammalian models of calorie restriction and extended longevity.

Mitochondrial hormesis is also involved in hypothermia, in which low temperatures can induce transient increases in ROS production. Hypothermia can stimulate longevity but has only been shown to induce an extended lifespan in lower animals, mainly *C. elegans* and Drosophila models (Baxter, Allard et al. 2014, Angstman, Frank et al. 2018). There are some studies suggesting that hypothermia is associated with increased ROS production in piglets (Langley, Chai et al. 2000), and lower levels of antioxidants in rats (Gamez, Alva et al. 2008) with decreases in oxygen availability (Alva, Palomeque et al. 2013) higher levels of malondialdehyde, a marker of oxidative stress, and lower levels of GSH, but no differences in the antioxidants, SOD and Gpx (Dede, Deger et al. 2002). Another rat study concluded

hypothermia causes oxidative stress with higher lipid peroxidation, lower activities of catalase, Gpx, and GSH, but higher SOD (Gumuslu, Sarikcioglu et al. 2002). However, there are also some studies that reported a reduction in oxidative stress as a result of hypothermia *in vitro* (Hasegawa, Ogihara et al. 2009), *ex vivo* (Mihara, Dohi et al. 2004) and *in vivo* from rats with brain injury, (Maier, Sun et al. 2002, Kuo, Lo et al. 2011), ischemia-reperfusion injury of skeletal muscle (Ozkan, Ekinci et al. 2015), and cardiac arrest in pigs (Ahn, Lee et al. 2020), (Gong, Li et al. 2012), (Ostadal, Mlcek et al. 2013).

Hypothermia is also an important protective mechanism in humans, e.g., hypothermia is used to protect patients in anesthesia and in critical care (Corry 2012). In addition, in a human study with cardiac arrest, therapeutic hypothermia reduced both reactive oxygen metabolites and antioxidant activity, whereas, the opposite is observed with rewarming, where both were increased (Dohi, Miyamoto et al. 2013).

This is consistent with well documented clinical observations of complete recovery of some patients with accidental hypothermia and cardiac arrest despite prolonged resuscitation (Giesbrecht 2000). These neuroprotective effects of hypothermia are now well recognized and therapeutic hypothermia is a common clinical tool in management of certain post-cardiac arrest patients (Rittenberger 2020). Another human study reported malondialdehyde is reduced and antioxidants levels are increased except for paraoxonase-1, in hypothermia patients compared to normothermia patients (Hackenhaar, Medeiros et al. 2017). It has also been shown that hypothermia can induce transient increases in ROS production in a variety of human cell lines (Brinkkoetter, Song et al. 2008, Hendriks, Bruggenwirth et al. 2019) and therefore can be speculated to activate similar adaptive responses leading to increases in longevity.

Blue Zones (Regions with Longer Lifespan in Their Inhabitants)

The goal of extending lifespan in humans has already been successful in certain parts of the world. Some countries like, Monaco, Japan and Switzerland have higher life expectancies than others (The-World-Factbook 2020). However, while it is tempting to attribute the long-life phenotype in these populations to their national origin or ethnicity, this is likely to be misleading because of the heterogeneity of life-style factors, even within individuals of a single country or ethnicity, which also profoundly affect longevity. Blue zones are relatively small regions where people routinely become centenarians. Rather than being limited to a nation or ethnicity, they are geographically widespread, and include locations in the United States, Costa Rica, the Mediterranean, and East-Asia (Buettner and Skemp 2016, Huang and Mark Jacquez 2017); for example, Loma Linda, USA; the Nicoya peninsula in Costa Rica; Sardinia, Italy; Ikaria, Greece; Okinawa, Japan (Buettner and Skemp 2016, Huang and Mark Jacquez 2017). In these areas the number of centenarians, i.e., those reaching the age of 100 is 10 times greater than the average in the United States. These regions are characterized by cultural preferences which discourage over-eating and excessive alcohol consumption, while encouraging active lifestyles. While the characteristics shared by these regions extend beyond diet and exercise, both a healthy diet and exercise training have been shown to reduce oxidative stress and protect against the deleterious effects of aging.

Common Specific Characteristics in Blue Zones

1. Ambulation: The inhabitants live in environments with motivation for frequent ambulation.
2. Healthy social relationships and psychological well-being: 1) many belong to some faith-based community, 2) seniors are valued members in their families and community, giving them a rich sense of purpose.
3. Diet: 1) 80% rule: stop eating when stomachs are 80% full; 2) Plant based diet: beans are the cornerstone of most centenarian diets. Meat is eaten on average only 5 times per month. 3) Drink alcohol moderately but regularly, 1–2 glasses per day, with friends and/or with food.
4. A cultural environment that reinforces healthy lifestyle and behavior.

VIII. Human Models of Reduced Longevity Associated with Increased Oxidative Stress

Perhaps the most convincing evidence for the role of oxidative stress in aging is progeria, a unique medical condition characterized by premature aging (Sinha, Ghosh et al. 2014). Teenagers with this condition often suffer from atherosclerosis, cardiomyopathy, coronary artery disease and premature death. The etiology involves the LMNA gene on chromosome 1q. Chromosome 1 is the largest human chromosome, and chromosome 1q is the q-arm on chromosome 1, which contains about 150 genes, one of these genes is LMNA, which encodes prelamin A. Prelamin A is ultimately converted to lamin A, a structural protein component of the nuclear lamina that stabilizes the nuclear membrane (Elzeneini and Wickström 2017). Pathogenic variants of LMNA cause degenerative disorders collectively known as laminopathies. The prototypical laminopathy is the classic Hutchinson-Gilford progeria syndrome (HGPS), which is commonly referred to simply as progeria. Accumulation of oxidized proteins causing DNA damage has been described as a causative mechanism in this disease (Berlett and Stadtman 1997, Lattanzi, Marmiroli et al. 2012).

Sources of oxidative stress include obesity, high fat diet or diets rich in sugar and processed foods, exposure to radiation, cigarette smoking, other tobacco products, alcohol consumption, certain medications, pollution, exposure to pesticides or industrial chemical and even oxygen itself. Supplemental oxygen can be deleterious, and in fact can contribute to increased mortality (Girardis, Busani et al. 2016, Chu, Kim et al. 2018). Both human and animal studies show that high concentrations of inspired oxygen can induce pulmonary complications, spanning from mild airway insult such as tracheobronchitis to severe parenchymal injury with diffuse alveolar damage that is histologically indistinguishable from acute respiratory distress syndrome (Hedley-Whyte 1970, Deneke and Fanburg 1980, Davis, Rennard et al. 1983). Excessive supplemental oxygen is also known to cause retinopathy of prematurity, an important cause of severe visual impairment in childhood. The etiology of retinopathy of prematurity involves low serum IGF-I values (Hellstrom, Perruzzi et al. 2001) which is associated with both suppression of vascular growth and proliferative retinopathy of prematurity (Hellstrom, Engstrom et al. 2003). Treating preterm infants with recombinant human (rh) IGF-I can prevent retinopathy of prematurity

(Hellström, Smith et al. 2013). Interestingly, the IGF-1R+/− Hetero mouse is a longevity model with protection against oxidative stress (Table I).

Metabolic syndrome is a serious clinical condition, comprised of a collection of cardiometabolic risk factors that includes obesity, insulin resistance, hypertension and dyslipidemia, mediated, in part, by increased oxidative stress (Roberts and Sindhu 2009, Mahjoub and Masrour-Roudsari 2012, Vona, Gambardella et al. 2019). Patients with metabolic syndrome have increased oxidative damage with increased lipid peroxidation malondialdehyde levels, protein carbonyls, and xanthine oxidase activity and decreased antioxidant protection, and decreased levels of antioxidant, e.g. superoxide dismutase activity, vitamin A, vitamin C, and carotenoids (Ford, Mokdad et al. 2003, Palmieri, Grattagliano et al. 2006, Armutcu, Ataymen et al. 2008). In addition, higher levels of oxidized low-density lipoproteins, carbonylation of cellular proteins, and NADPH oxidase activity, which induce oxidative stress, are associated with metabolic syndrome (Holvoet, Lee et al. 2008, Vona, Gambardella et al. 2019).

Cigarette smoking is another cause of increased ROS and decreased antioxidant status in tissues, and similarly, fine particulate matter in polluted air is also associated with increased ROS and oxidative stress (Lodovici and Bigagli 2011, Jansen EHJM, Beekhof P et al. 2014). According to the CDC, the life expectancy for smokers is at least 10 years shorter than for nonsmokers (Jha, Ramasundarahettige et al. 2013, NCCDPHP 2014).

Almost all of the diseases that limit longevity and healthful aging are associated with increased oxidative stress, e.g., myocardial infarction (Zweier and Talukder 2006), heart failure (Tsutsui, Kinugawa et al. 2011), exercise intolerance (Witman, McDaniel et al. 2012), hypertension (Rodrigo, Gonzalez et al. 2011), cancer (Reuter, Gupta et al. 2010), neurological diseases, e.g., Alzheimer’s Disease and Parkinson’s Disease (Uttara, Singh et al. 2009, Patel 2016) and metabolic syndrome (Vona, Gambardella et al. 2019), diabetes (Giacco and Brownlee 2010), obesity (Manna and Jain 2015) and hyperlipidemia (Yang, Shi et al. 2008). There are two important points; 1) all of these diseases limit healthful aging beyond limiting only lifespan, and 2) many of these diseases of aging are linked to others, augmenting the negative impact of oxidative stress on healthful aging.

Increased β-adrenergic signaling is a major mechanism increasing oxidative stress and mediating reduced longevity, as it results in increased myocardial oxygen consumption, which in the presence of atherosclerosis or hypertension leads to myocardial ischemic disease and heart failure, major causes of disability and death in the older population. Increased β-adrenergic signaling via chronic administration of β-adrenergic receptor agonists increase morbidity and mortality in humans and other mammals (Ho, Yan et al. 2010).

Conversely, low resting heart rate, a key feature of reduced β-adrenergic signaling is associated with healthful longevity (Jensen 2019). There are physiological methods to reduce increased β-adrenergic signaling, e.g., exercise and weight loss. There are also many therapeutic modalities to reduce increased β-adrenergic signaling. Most commonly β-adrenergic blocking drugs are administered to patients to accomplish this, e.g., metoprolol or

bisoprolol. β-adrenergic receptor blockade therapy has become increasingly important in the aging population, since it decreases mortality after acute myocardial infarction and chronic stable angina post-myocardial infarction (Gibbons, Chatterjee et al. 1999), and protects against hypertension (Wiysonge and Opie 2013) and reduces both the incidence and severity of Alzheimer's Disease (Bristow 2000, Rosenberg, Mielke et al. 2008). β-adrenergic receptor blockade therapy also reduces mortality in type 2 diabetics with concomitant hypertension (UK-Prospective-Diabetes-Study-Group 1998), heart failure (Bell, Lukas et al. 2006), or myocardial infarction (Gottlieb, McCarter et al. 1998). On the other hand, these drugs have major adverse side effects including decreased cardiac output, increased airway resistance which can worsen asthma, exacerbation of peripheral vascular disease, and sexual dysfunction. These drugs also alter glucose metabolism and lead to hypoglycemia and are associated with weight gain. Accordingly, new pharmaceutical modalities are required to alleviate enhanced β-adrenergic signaling and protect against oxidative stress.

One approach to develop new pharmacological agents to reduce β-adrenergic signaling, can be derived from prior sections in this review involving longevity models, particularly the adenylyl cyclase type 5 KO mice, which have decreased β-adrenergic signaling, resulting in increased maximal lifespan (Yan, Vatner et al. 2007). This is further supported in humans, in which individuals with the genetic haplotype A-C, a known haplotype of decreased β_2AR signaling, were more likely to become centenarians (Zhao, Yang et al. 2012).

Summary

Protection against oxidative stress is a major mechanism mediating increased longevity. Other mechanisms mediating increased longevity are summarized in Table II and include exercise, protection against obesity, increased β-adrenergic signaling, and against concomitant diseases of aging, e.g., diabetes, cancer, cardiovascular diseases, and neurological diseases including Alzheimer's Disease. This review describes the animal models of increased longevity, relating these findings to human longevity. The review of these animal models identifies gaps in knowledge to facilitate further research and drug development. New pharmacologic agents could be designed based on any of the healthful longevity models noted in Table II.

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Highlights:

- The role of protection against oxidative stress mediating longevity and more importantly, healthful aging.
- The role of protection against those debilitating diseases that are prevalent in the elderly and negatively impact healthful aging, e.g., diabetes and other metabolic diseases, obesity, cancer, neurological diseases, aging-induced cardiomyopathy, cardiac stress, osteoporosis and reduced exercise capacity and increased β-adrenergic signaling.
- The common cellular signaling pathways involved in protection against oxidative stress in aging and in the associated diseases of aging

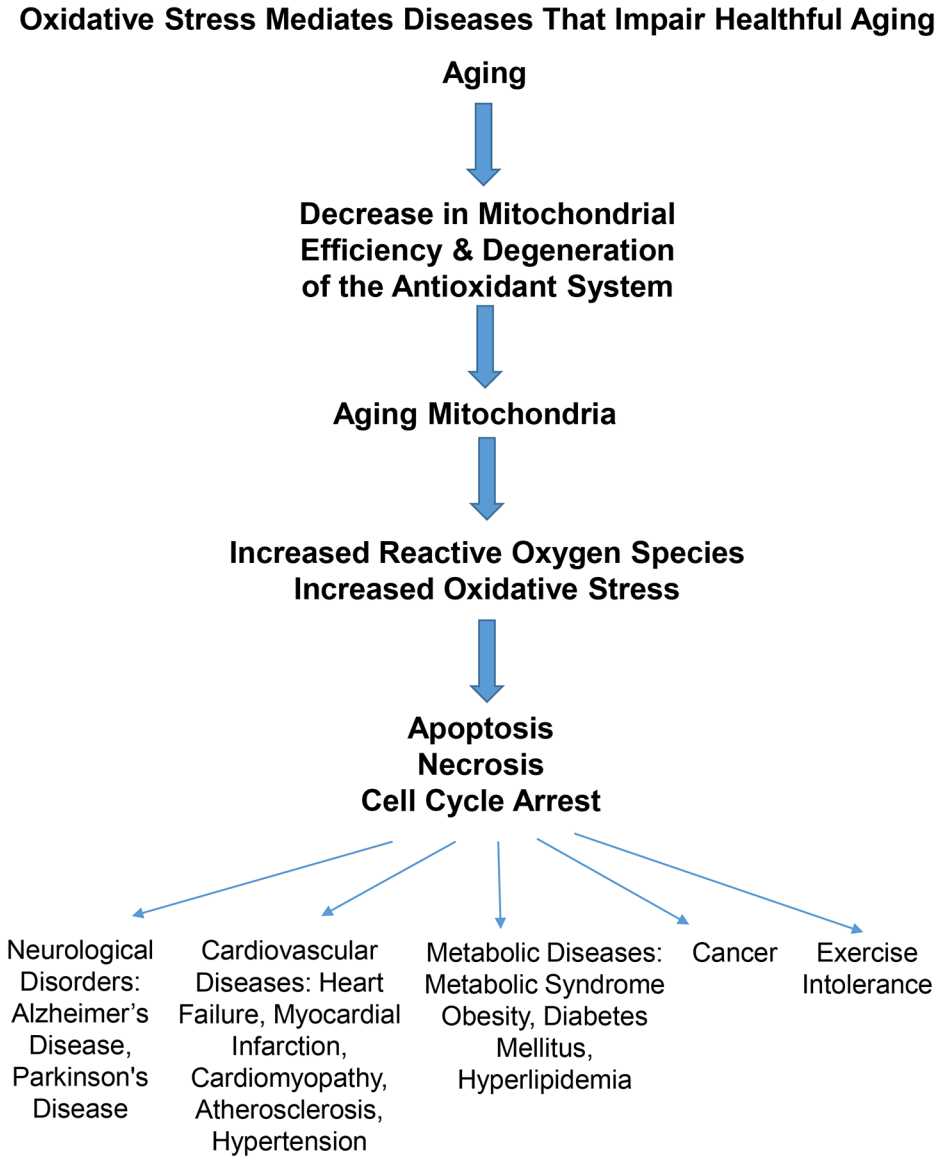

Figure 1:

In aging, mitochondrial dysfunction and degeneration of the antioxidant system induce production of reactive oxygen species, which result in increased oxidative stress and cell dysfunction and death (e.g. apoptosis, necrosis, and cell cycle arrest). These deficiencies are involved in mediation of neurological disorders, cardiovascular diseases, metabolic disorders, exercise intolerance and cancer.

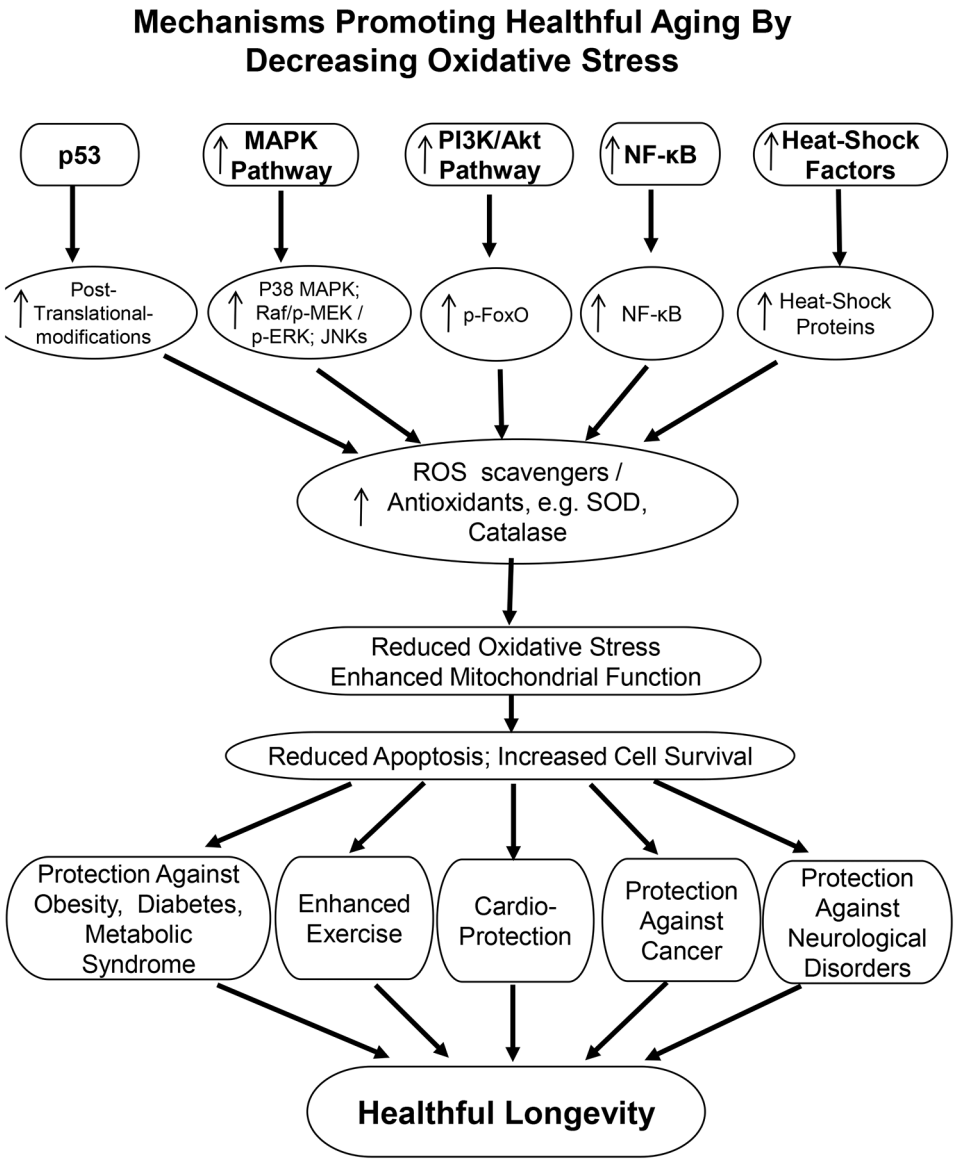

Figure 2:

Activated MAPK, PI3K/Akt pathways, NF-κB, and heat-shock factors lead to upregulation of their downstream pathways, all acting to increase anti-oxidants, which then reduce oxidative stress and increase mitochondrial function, resulting in increased cell survival and healthful longevity. p53 has dual roles in oxidative stress. In this figure, under low oxidative stress condition, p53 activation provides an antioxidant defense to protect against oxidative stress.

Table I:

Oxidative Stress Protection in Longevity Models

Longevity Model	Median Survival Age Wild Type (Months)	% Increase Lifespan Compared to Wild Type
Longevity Models with Known Protection Against Oxidative Stress		
Calorie Restriction	30	Up to 50
Snell Dwarf	18	50
Adenylyl Cyclase Type 5 Knockout (AC5 KO)	25	32
Growth Hormone Receptor Knockout (GHR KO)	27	31
p66 SHC-Transforming Protein 1 (p66 shc) Knockout	26	30
Angiotensin II Receptor Type 1 Alpha Knockout (Agtr1 α−/− KO)	26	26
Regulator of G Protein Signaling 14 Knockout (RGS14 KO)	23	26
Insulin-like Growth Factor Type 1 Receptor Hetero (IGF-1R+/− Hetero)	21	24
Klotho Overexpression	32	22
Mitochondrial Targeted Catalase (MCAT) Overexpression	25	19
Ribosomal Protein S6 Kinase β−1 (S6K1) Knockout	28	19
A Longevity Model Not Protected Against Oxidative Stress		
Growth Hormone Receptor/Binding Protein Knockout (GHR/BP KO)	23	47
Longevity Models With Oxidative Stress Protection Controversial		
Ames Dwarf	21	57
Mitochondrial 5-Demethoxyubiquinone Hydroxylase Hetero (Mclk1+/−)	22	31
Insulin Receptor Substrate 1 Knockout (IRS1 KO)	24	18
Longevity Models With Oxidative Stress Not Studied		
Phosphoenolpyruvate Carboxykinase (PEPCK-C) Overexpression	Age unspecified, but the mice still reproduce after age 30 months	
Pregnancy-Associated Plasma Protein-A Knockout (PAPPA KO)	21	26

Table II-a:

Protective Features of Longevity Models Protected Against Oxidative Stress

MODEL	IMPROVED EXERCISE	OBESITY PROTECTION	DIABETES PROTECTION	CV STRESS PROTECTION	CANCER PROTECTION	PROTECTION OBSERVED IN OLD AGE	DECREASED β-ADRENERGIC SIGNALING
Human Models of Longevity	+	+	+	+	+	+	+
Calorie Restriction	−	+	+	+	+	+	−
Snell Dwarf	?	+/−	+	?	+	+	−
Adenylyl Cyclase 5 KO	+	+	+	+	+	+	+
Growth Hormone Receptor (GHR) KO	?	−	+	+	+	?	?
p66shc Protein KO	+/−	+/−	+	+	+	−	?
Angiotensin II Receptor Type 1 alpha (Agtr1α) KO	?	+	?	+/−	+	?	?
Regulator of G Protein Signaling 14 KO	+	+	+	+	+	+	+
Insulin Like Growth Factor Type 1 Receptor +/−	?	+/−	−	?	+/−	?	?
Klotho Overexpression	?	+	−	+	+	−	?
Mitochondrial Targeted Catalase (MCAT) Overexpression	+	−	+	+	+	+/−	+
Ribosomal Protein S6 Kinase β-1 (S6K1) KO	+	+	+	?	+	+	?

Table II-b:

Protective Features of A Longevity Model Not Protected Against Oxidative Stress

MODEL	IMPROVED EXERCISE	OBESITY PROTECTION	DIABETES PROTECTION	CV STRESS PROTECTION	CANCER PROTECTION	PROTECTION OBSERVED IN OLD AGE	DECREASED β-ADRENERGIC SIGNALING
Growth Hormone Receptor and Binding Protein KO	+	+	?	?	+	+	?

Table II-c:

Protective Features of Longevity Models With Oxidative Stress Protection Controversial

MODEL	IMPROVED EXERCISE	OBESITY PROTECTION	DIABETES PROTECTION	CV STRESS PROTECTION	CANCER PROTECTION	PROTECTION OBSERVED IN OLD AGE	DECREASED β-ADRENERGIC SIGNALING
Ames Dwarf	?	−	+	+	+	+/−	?
Mitochondrial 5-Demethoxyubiquinone Hydroxylase Hetero (Mclk1+/−)	?	?	?	?	+	?	?
Insulin Receptor Substrate 1 KO	?	+	−	−	+/−	+/−	+

Table II-d:

Protective Features of Longevity Models With Oxidative Stress Not Studied

MODEL	IMPROVED EXERCISE	OBESITY PROTECTION	DIABETES PROTECTION	CV STRESS PROTECTION	CANCER PROTECTION	PROTECTION OBSERVED IN OLD AGE	DECREASED β-ADRENERGIC SIGNALING
Phosphoenolpyruvate Carboxykinase (PEPCK-C) Overexpression	+	+	−	?	?	+	?
Pregnancy Associated Protein Plasma A KO	?	+/−	+	?	+	?	?

Table II:+: positive results, −: negative results; +/−: controversial results; ?: not studied.