Mitochondria and Cardiovascular Aging

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Abstract: Old age is a major risk factor for cardiovascular diseases. Several lines of evidence in experimental animal models have indicated the central role of mitochondria both in lifespan determination and in cardiovascular aging. In this article we review the evidence supporting the role of mitochondrial oxidative stress, mitochondrial damage and biogenesis as well as the crosstalk between mitochondria and cellular signaling in cardiac and vascular aging. Intrinsic cardiac aging in the murine model closely recapitulates age-related cardiac changes in humans (left ventricular hypertrophy, fibrosis and diastolic dysfunction), while the phenotype of vascular aging include endothelial dysfunction, reduced vascular elasticity, and chronic vascular inflammation. Both cardiac and vascular aging involve neurohormonal signaling (eg, renin–angiotensin, adrenergic, insulin-IGF1 signaling) and cell-autonomous mechanisms. The potential therapeutic strategies to improve mitochondrial function in aging and cardiovascular diseases are also discussed, with a focus on mitochondrial-targeted antioxidants, calorie restriction, calorie restriction mimetics, and exercise training. (Circ Res. 2012;110:1109-1124.)

Key Words: senescence • oxidative stress • heart • aorta • microcirculation

Mitochondria play important roles in a myriad of cellular processes including ATP production via oxidative phosphorylation, biosynthetic pathways, cellular redox homeostasis, ion homeostasis, oxygen sensing, signaling, and regulation of programmed cell death. Mitochondrial dysfunction is central to theories of aging, because age-related changes of mitochondria are likely to impair a host of cellular physiological functions in parallel and contribute to the development of all common age-related diseases.

Age-specific mortality rates from heart disease and stroke and the incidence of peripheral vascular disease and vascular cognitive impairment increase exponentially with age in people over 65 years of age. Previous studies established that mitochondria have a central role in age-related pathological alterations of the heart. In addition, there is growing evidence that mitochondria have also an important role in vascular pathophysiology. Development of novel therapeutic approaches for mitochondrial rejuvenation and attenuation of...
mitochondrial oxidative stress holds promise for reducing cardiovascular mortality in an aging population. In this review, the effects of aging on mitochondrial function and phenotype in the cardiovascular system and the signaling role of mitochondria in aging are considered. The possible benefits of therapeutic strategies that have the potential to improve mitochondrial function and delay the onset of age-related cardiovascular diseases are also discussed. The review is organized into 4 sections: (1) mitochondrial oxidative stress and aging; (2) mechanisms and signaling pathways mediating mitochondrial effects of cardiac aging; (3) therapeutic strategies to improve mitochondrial function in aging; and (4) perspectives.

**Mitochondrial Oxidative Stress Theory and Aging**

**The Free Radical Theory of Aging**

First proposed by Harman in 1956, the free radical theory of aging postulates that the production of intracellular reactive oxygen species (ROS) is the major determinant of lifespan. Decline in cellular and organ functions as well as the associated degenerative diseases in old age could be attributed to deleterious effects of ROS on various cellular components. ROS are generated in multiple compartments and by multiple enzymes within the cell, such as NADPH oxidase at the plasma membrane, lipid oxidation within peroxisomes, oxidative phosphorylation within mitochondria, and various cyclooxygenases and xanthine oxidase in the cytoplasm. Although all of these sources contribute to the overall oxidative burden, the majority of ROS are produced during oxidative phosphorylation and ATP generation within the mitochondria in aging. This has led to the extension of free radical theory in the 1970s to implicate mitochondrial production of ROS (including superoxide [O$_2^-$] and hydrogen peroxide [H$_2$O$_2$]) as the main cause for age-related damage and degeneration. Mitochondrial ROS might attack various mitochondrial constituents, causing mitochondrial DNA mutations and oxidative damage to respiratory enzymes. A defect in mitochondrial respiratory enzymes would increase mitochondrial production of ROS, causing further mitochondrial damage and dysfunction, leading to further decline in cellular and organ function that can eventually progress to death. A large body of evidence has been published both in support of and against the free radical theory of aging. Key observations have been the lack of concordance between expected and observed results in knockout and transgenic mouse models. Knockout mice for major cellular antioxidant enzymes show a relatively mild phenotype and rarely demonstrate a lifespan decrease despite significant increases in ROS. Conversely, overexpression of antioxidant enzymes has generally failed to extend mouse lifespan. In accord with this, oral antioxidant supplementation in humans with good nutritional status has generally not been shown to produce beneficial effects. However, the mitochondrial variant of the free radical theory of aging, which postulates that free radical generated by mitochondria is the main determinant of lifespan, has not been nearly as well tested. As described below, there is evidence that reducing mitochondrial ROS has lifespan and cardiac health benefits.

**Mitochondrial Oxidative Stress in Cardiac Aging**

Considerable evidence has been published that with advanced age mitochondrial production of ROS significantly increases both in the heart and the vasculature. Age-dependent mitochondrial dysfunction is closely correlated with abnormal mitochondrial ROS production and detoxification (reviewed by Mammucari & Rizzuto, Trifunovic & Larsson, and Terzioglu & Larsson). For example, an age-dependent reduction in mitochondrial oxidative phosphorylation is associated with the decline in mitochondrial state 3 respiration (maximal ADP-stimulated respiration in the presence of excess substrates) due to diminished activity of electron transport by complexes I and IV, which include critical components encoded by mitochondrial DNA. The complexes II, III, and V are believed to be less affected in aging (see review by Navarro & Boveris). Such impairment of electron transport function might be directly related to elevated electron leakage and generation of mitochondrial ROS.
The heart is a vital organ with high metabolic demand and rich in mitochondria, and since ROS is produced in mitochondria as a byproduct of oxidative phosphorylation, the heart is especially prone to oxidative damage. Direct evidence of the critical role of mitochondrial ROS in aging was demonstrated in mice overexpressing catalase targeted to the mitochondria (mCAT), which had 18% prolongation of lifespan when compared with wild-type (WT) littermates, whereas mice overexpressing catalase targeted to peroxisomes (pCAT, the natural site of catalase) or the nucleus had little or no lifespan extension. Work in the Rabinovitch laboratory further showed that mCAT mice were protected from the phenotypes of cardiac aging. Cardiac aging in mice closely recapitulates those found in human cardiac aging, as shown in Table 1 which include age-dependent increase in echocardiographic left ventricular mass index (LVMI, \( P < 0.01 \) for age-dependent change), a modest decline in systolic function with age (FS%, \( P = 0.03 \)) and a significant decline in diastolic function measured by Ea/Aa (\( P < 0.01 \)) as well as impairment of myocardial performance with age, indicated by increase in myocardial performance index (indicated a greater fraction of systole was spent during isovolumic contraction and relaxation, \( P < 0.01 \)). Furthermore, the proportion of mice with diastolic dysfunction and left atrium dilatation also significantly increased with age. All of the above phenotypes of cardiac aging were significantly attenuated in mCAT mice (Table 1, \( P < 0.01 \) for old WT versus old mCAT). Consistent with this, mitochondrial oxidative damage was increased in the aged hearts, as supported by an increase in mitochondrial protein carbonyls and a greater than 6-fold increase in mitochondrial DNA deletions (Table 1), and consistent with this, the activation of PGC-1α and the increase in mtDNA copy number in aging was also attenuated.

The success of targeted, specific ROS scavenging intervention by mCAT suggests that a key to successful intervention lies in specificity. Given the complexity of the systems involved, it seems possible that mitochondrial dysfunction and aberrant ROS production may contribute to aging through interference with normal signaling and energetics as much, or more than, by the direct damaging effect to cellular macromolecules. Age-dependent decline in the rate of mitochondrial electron transfer also favors mitochondrial superoxide production, leading to a positive feedback between complex I inhibition and mitochondrial ROS production, as well as the more classical vicious cycle of mitochondrial DNA mutation and protein damage amplifying ROS. When viewed in the light of alterations in both signaling and energetics, this may be a critical factor in cardiac (and other organ system) aging (Figure 1).

Further evidence supporting the role of mitochondria in aging was demonstrated using mice with homozygous mutation of mitochondrial polymerase gamma (Polg\(^{−/−}\)) and the increase in mtDNA point mutations and deletions with age. These mice have shortened lifespan (maximal lifespan \( \approx 15 \) months) and several progeroid phenotypes, including kyphosis, gray hair, and several progeroid phenotypes, including kyphosis, gray hair, osteoporosis, sarcopenia (loss of muscle mass), and presbycusis (age-related hearing loss). It has been shown that accumulation of mtDNA deletions is better correlated with the “premature” aging-like phenotype in these mice than are mtDNA point mutations. The accumulation of mitochondrial DNA damage has been shown to increase apoptotic rate as well as mitochondrial oxidative damage in the mouse heart (Table 1). Cardiomyopathy is evident in middle-aged (13–14 months) Polg\(^{−/−}\) mice, to a degree that is much more severe than the usual cardiac aging in WT mice. Cardiac hypertrophy, as indicated by LVMI, is much greater in Polg\(^{−/−}\) mice in middle age than in WT mice of 24 to 30 months old (Table 1). Likewise, systolic and diastolic function in Polg\(^{−/−}\) mice is also worse than the usual cardiac aging (Table 1). The observations that mitochondrial damage and cardiomyopathy in these mice can be partially rescued by mCAT (Table 1) suggests that mitochondrial ROS and mitochondrial DNA damage are part of a vicious cycle of ROS-induced ROS release (Table 1). Interestingly, a recent paper reports the striking observation that endurance exercise in Polg\(^{−/−}\) mice can prevent both their skeletal muscle and cardiac progeroid phenotypes. The authors suggest that increased level of mitochondrial biogenesis seen with exercise in these mice is a critical factor in maintaining mitochondrial and organ function. Additional implication of mitochondria in cardiac aging comes from observations of mice with a...
targeted mutation of the p66<sup>Shc</sup> gene. These mice display prolonged lifespan, reduced production of ROS, and increased resistance to ROS-mediated apoptosis. The p66<sup>Shc</sup> localizes to the mitochondrial intermembranous space and has been shown to be a mitochondrial redox enzyme, forming ROS by using electrons from the respiratory chain to produce H<sub>2</sub>O<sub>2</sub>. A recent study from the same group showed that p66<sup>Shc</sup> was phosphorylated by PKC-beta together with prolyl isomerase Pin-1, then the phosphorylated p66<sup>Shc</sup> accumulated within mitochondria to activate mitochondrial Ca<sup>2+</sup> response, and subsequently induce apoptosis. Disruption of p66<sup>Shc</sup> prevents angiotensin II–induced LV hypertrophy and cardiomyocytes apoptosis as well as reducing oxidative damage in cardiac progenitor cells, cardiomyocytes, and endothelial cells in a diabetic mouse model.

Consistent with all of the above, a deficiency of mitochondrial energetics has been documented in human and experimental animals with heart failure. Mechanisms may include mitochondrial biogenesis that does not keep up with the increasing demand (see review by Goffart et al), mitochondrial uncoupling and decreased substrate availability, and increased mitochondrial DNA deletions.

**Mitochondrial Oxidative Stress in Vascular Aging**

There is growing evidence that increased mitochondrial production of ROS also has an important role in age-related vascular impairment. Previous studies suggest that increased ROS in aging promotes mitochondrial protein oxidation and increased mitochondrial DNA mutations in the heart and other organs, but it is yet to be determined whether similar aging-induced mitochondrial DNA and protein damage plays an important role in vascular endothelial and smooth muscle cells. Importantly, mitochondria-derived ROS are likely to contribute to the development of chronic low-grade vascular inflammation in aging by activating redox signaling pathways (see below). Furthermore, recent studies suggest that mitochondria-derived ROS contribute to accelerated development of the senescent phenotype in endothelial cells (ie, by activating Akt). Endothelial cell senescence may impair the regenerative and angiogenic capacity of the endothelium, its reactivity and promote the progression of atherosclerosis by altering the secretion of cytokines, growth factors, and proteases in the vascular wall. Another potentially important link between mitochondrial oxidative stress and vascular aging is the induction of apoptosis. Oxidative stress in aging is associated with an increased rate of endothelial apoptosis, which may contribute to microvascular rarefaction impairing the blood supply of the heart and the brain. Cerebrovascular endothelial cells are rich in mitochondria, and normal mitochondrial function is essential for maintaining the integrity of the blood–brain barrier. On the basis of the available data with mitochondrial inhibitors, we posit that age-related mitochondrial dysfunction may contribute to breakdown of the blood–brain barrier, promoting neuroinflammation in aging. Mitochondrial-derived ROS may also impact endothelium-dependent vasodilation.

**Figure 1. Proposed signaling mechanism of angiotensin/Gq and mitochondrial ROS amplification in aging and cardiovascular diseases.** AT1-R, angiotensin receptor-1; Nnt, nicotinamide nucleotide transhydrogenase. Illustration credit: Cosmocyte/Ben Smith.
vasodilator function in the aged vasculature, or maintain the integrity of the blood–brain barrier.

**Mechanisms and Signaling Pathways Mediating Mitochondrial Effects of Cardiovascular Aging**

**Molecular Mechanisms Contributing to Mitochondrial Oxidative Stress in the Aging Cardiovascular System**

The molecular mechanisms underlying age-related increases in mitochondrial oxidative stress in the cardiovascular system are multifaceted and likely involve cell-autonomous effects, including a significant decline in reduced glutathione content, dysregulation of antioxidant defense mechanisms (e.g., peroxyxnitrite-mediated nitration and inhibition of MnSOD), and a dysfunctional electron transport chain. Furthermore, there is also evidence that a cross-talk exists between mitochondrial and cytosolic sources of ROS production (see below). There is a significant age-related increase in NADPH oxidase activity both in heart and vasculature, which is likely to exacerbate mitochondrial oxidative stress in aging. In addition to the aforementioned age-related mechanisms, several cardiovascular risk factors—including oxidatively modified lipoproteins, cigarette smoke constituents, high methionine diet and hyperhomocysteinemia, and diabetes—either directly or indirectly may increase ROS production in mitochondria of vascular cells and cardiac myocytes. Recent studies suggest that age-related changes in endocrine/paracrine regulatory mechanisms—including activation of the renin–angiotensin–aldosterone system, adrenergic signaling, and an age-related dysfunction of growth hormone/IGF-I signaling—also have an important role in promoting mitochondrial oxidative stress in the aged cardiovascular system.

**Renin–Angiotensin–Aldosterone System**

The renin–angiotensin–aldosterone system is the key player implicated in a broad spectrum of cardiovascular diseases, including hypertension, coronary heart disease, and congestive heart failure, as well as atrial fibrillation. The prevalence of these diseases has been shown to increase with age in the American Heart Association Heart Disease and Stroke Statistics update. Indeed, both renin and angiotensin II (Ang II) have been shown to induce cardiac hypertrophy and cardiomyocytes apoptosis, increases cardiac fibrosis, and impairs cardiomyocyte relaxation. All of the above changes are compatible with the phenotypes associated with cardiac aging. The concentration of Ang II in cardiac tissue has been shown to increase significantly in aged rodent hearts, which is presumably related to increase in local angiotensin II converting enzyme (ACE) level in cardiac and vascular tissues. Although the mechanism of increased ACE in aging is not well understood, long-term inhibition with angiotensin receptor blockers or disruption of angiotensin receptor type I has been shown to reduce age-dependent cardiac pathology and prolong rat and mouse survival. Thus, the activation of renin–angiotensin system might play a central role in cardiac aging and age-associated cardiovascular diseases. At the molecular level, angiotensin has been shown to induce an increase in total cellular and mitochondrial ROS, and it is likely that angiotensin II–induced mitochondrial ROS is the proximal mediator of cardiac aging changes. The mechanistic relationship of angiotensin II and mitochondria in cardiac hypertrophy and failure is discussed below.

**Adrenergic Signaling**

It is well accepted that chronic stimulation of adrenergic signaling by catecholamine is deleterious to the heart, as this activation increased heart rate, contractility, afterload (blood pressure), and cardiac wall stress, which subsequently increases cardiac metabolic demand. Adenylate cyclase is a key enzyme producing c-AMP as a secondary messenger downstream to β-adrenergic signaling, and adenylate cyclase type 5 (AC5) is the major form in the heart. Disruption of AC5 has been shown to protect against chronic pressure overload-induced cardiac hypertrophy, apoptosis, and failure by chronic catecholamine stimulation or aortic banding. These animals were shown to have prolonged lifespan, which might be mediated through upregulation of Raf-1/pMEK/pERK pathway, which confers protection against oxidative stress. Furthermore, AC5 knock-out mice were also shown to attenuate aging changes in the heart, including cardiac hypertrophy, systolic dysfunction, apoptosis, and fibrosis. Although several clinical trials have shown the efficacy of specific β-blockers to provide survival benefit in patients with heart failure, the effects of β-blockers on human cardiac aging are yet to be determined.

Emerging evidence has shown that activation of adrenergic signaling could induce mitochondrial ROS. Chronic β-adrenergic stimulation induces mitochondrial membrane depolarization and apoptosis in adult rat cardiomyocytes that is inhibited by Mn-SOD/catalase mimetics and by overexpression of catalase. Furthermore, in vitro stimulation of the β-adrenergic receptor also induces mitochondrial ROS in mouse neonatal ventricular cardiomyocytes via cAMP-PKA pathways. A recent study demonstrated that β-adrenergic stimulation induced increase in cardiomyocytes Ca2+ transient amplitude was diminished by the antioxidant N-acetyl cysteine as well as the mitochondrial-targeted antioxidant SS31. The above findings support the significant role in mitochondrial ROS in β-adrenergic signaling.

**Growth Hormone and IGF1 Signaling**

Previous studies suggest that a causal relationship exists among declining levels of insulin-like growth factor-I and growth hormone (GH, which regulates the synthesis of IGF-1) and age-related cardiovascular morbidity and mortality in humans and in laboratory animals (for a review, see Khan et al). There is increasing evidence that the beneficial cardiovascular effects of IGF-1, at least in part, can be related to mitochondrial protection mechanisms. Importantly, treatment of cultured endothelial cells and cardiomyocytes with IGF-1 decreases mitochondrial superoxide production. Furthermore, low plasma levels of GH and IGF-1 in Ames dwarf mice (which exhibit defective development of the pituitary gland due to a mutation in Prop-1) are associated with increased mitochondrial oxidative stress both in the vasculature and the heart, mimicking the aging phenotype (Table 2). Interestingly, mitochondrial oxidative stress in the heart of Ames dwarf mice appears to be associated with impaired
Table 2. Influence of Genetic and Pharmacological Manipulations Related to Mitochondria on Aging and Cardiovascular Phenotypes in Rodent Models

<table>
<thead>
<tr>
<th>Animal Models</th>
<th>Description</th>
<th>Aging Phenotypes</th>
<th>Cardiovascular Phenotypes</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>mCAT</td>
<td>Overexpression of catalase targeted to mitochondria.</td>
<td>18% extension of lifespan. Attenuated cardiac aging, aging-related sarcopenia, presbyacusis, and cancer incidence.</td>
<td>Protect against cardiac hypertrophy and heart failure.</td>
<td>11, 12, 27, 94, 142</td>
</tr>
<tr>
<td>Polg&lt;sup&gt;gmc&lt;/sup&gt;</td>
<td>Homozygous mutation of mitochondrial polymerase gamma D257A.</td>
<td>“Accelerated aging”: sarcopenia, graying and alopecia, kyphosis, presbyacusis, anemia, age-dependent cardiomyopathy.</td>
<td>Aggravate heart failure in response to angiotensin II.</td>
<td>13, 14, 16, 18, 27</td>
</tr>
<tr>
<td>p66&lt;sup&gt;hsc&lt;/sup&gt;</td>
<td>Targeted mutation of the p66&lt;sup&gt;hsc&lt;/sup&gt; gene.</td>
<td>Extension of lifespan. Reduction of ROS and apoptosis.</td>
<td>Attenuate angiotensin II induced LV hypertrophy and cardiomyocytes apoptosis; reduce oxidative damage in cardiac progenitor cells, cardiomyocytes and endothelial cells in diabetes.</td>
<td>18, 20–22</td>
</tr>
<tr>
<td>Tg-Sirt1</td>
<td>α-myosin heavy chain (α-MHC) promoter-driven, cardiac-specific overexpression of SIRT1.</td>
<td>Delayed cardiac aging.</td>
<td>Attenuates age-dependent increases in cardiac hypertrophy, apoptosis/fibrosis, cardiac dysfunction, and expression of senescence markers; reduces myocardial infarction/area at risk after ischemia/reperfusion.</td>
<td>143, 144</td>
</tr>
<tr>
<td>Sirt1&lt;sup&gt;flx/flx&lt;/sup&gt;,&lt;sup&gt;α-MHC-Cre&lt;/sup&gt;</td>
<td>Cardiac-specific Sirt1&lt;sup&gt;−/−&lt;/sup&gt; mice.</td>
<td></td>
<td>Increases size of myocardial infarction after ischemia/reperfusion.</td>
<td>144</td>
</tr>
<tr>
<td>SIRT3&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>SIRT3-deficient mice.</td>
<td>Accelerated cardiac aging, age-dependent increase in mitochondrial swelling due to increased mPTP opening.</td>
<td>Early-age onset of hypertrophy associated with fibrosis, increased mortality after transaortic constriction.</td>
<td>117</td>
</tr>
<tr>
<td>Nrf2&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>Nrf2-deficient mice.</td>
<td>Pathological cardiac hypertrophy, myocardial fibrosis and apoptosis, overt heart failure, and increased mortality after transaortic constriction; exacerbation of high-fat-diet-induced endothelial dysfunction and vascular oxidative stress and inflammation.</td>
<td>123, 145, 146</td>
<td></td>
</tr>
<tr>
<td>Tg-IGF-1</td>
<td>Cardiac-specific overexpression of IGF-1.</td>
<td>Attenuates aging-associated cardiac diastolic contractile dysfunction.</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>Prop1df/Prop1df</td>
<td>GH- and IGF-1 deficient Ames dwarf mice.</td>
<td>Extension of lifespan due to reduced cancer incidence.</td>
<td>Mitochondrial oxidative stress in vasculature and the heart; cardiac dysfunction.</td>
<td>56, 57</td>
</tr>
<tr>
<td>dw-4/dw-4</td>
<td>GH- and IGF-1 deficient Lewis dwarf rats.</td>
<td>Increased incidence of stroke, no change in lifespan.</td>
<td>Vascular oxidative stress, increased high-fat-diet-induced vascular inflammation.</td>
<td>148, 149</td>
</tr>
<tr>
<td>Igf1&lt;sup&gt;−/−&lt;/sup&gt; + MUP-iCre-AAV8</td>
<td>AAV-mediated hepatic knockdown of IGF-1.</td>
<td></td>
<td>Impaired vascular oxidative stress resistance, Nrf2 dysfunction, increased apoptosis.</td>
<td>150</td>
</tr>
</tbody>
</table>

(Continued)
In addition, dysfunction of the proteasomes may also likely contribute to the accumulation of damaged non-mitochondrial proteins in mitochondria (including the mitochondrial DNA) are particularly susceptible to oxidative damage, effective control of mitochondrial turnover is critical to the maintenance of a healthy mitochondrial phenotype, normal energy production, and the promotion of healthy aging. Mitochondria are highly dynamic organelles, and dysregulation of mitochondrial turnover is likely one of the intrinsic causes of mitochondrial dysfunction, which contributes to dysregulation of cell metabolism, oxidative stress, and altered signal transduction during the aging process.

**Autophagy** is a catabolic process that contributes to the maintenance of cellular homeostasis in the cardiovascular system through the degradation of damaged mitochondria in lysosomes. In the heart of young mice angiotensin II–induced mitochondrial oxidative stress mediates induction of autophagy and mitochondrial biogenesis, likely to replenish the damaged mitochondria and restore energy production. The available evidence suggest that there is an age-dependent decline in autophagic function, which likely contributes to the accumulation of damaged non-functional mitochondria in the heart and the vasculature. In addition, dysfunction of the proteasomes may also contribute to the accumulation of damaged mitochondrial proteins in the aged cardiovascular system.

Previous studies demonstrate that mitochondrial biogenesis increases in the aged heart, as indicated by the increase in contractile function. Recent studies show that treatment of aged rodents with IGF-1 confers mitochondrial protection, including an attenuation of mitochondrial ROS generation in the liver. The available data suggest that treatments that increase circulating IGF-1 levels exert cardiovascular protective effects in aging. Thus, further studies are warranted to determine the role of mitochondrial mechanisms in the beneficial effects of GH replacement and IGF-1 treatment in the aged heart and vasculature, including the effects of IGF-1 on autophagy of dysfunctional mitochondria and apoptosis.

**Age-Related Nrf2 Dysfunction**

In the heart and the vasculature of young animals in response to increased production of mitochondria-derived ROS an adaptive NF-E2-related factor 2 (Nrf2)–driven antioxidant defense mechanism manifests, which upregulates antioxidant response element (ARE)–driven expression of detoxifying and antioxidant enzymes and the cystine/glutamate transporter involved in glutathione biosynthesis. This homeostatic response serves to attenuate oxidative stress in the mitochondria and the cytoplasm and limit the cellular dysfunction caused by the increased production of ROS. Recent findings demonstrate that in aging vessels increased production of ROS by mitochondria and other sources fails to activate Nrf2 resulting in increased cellular sensitivity to the deleterious effects of oxidative stressors (Table 2). In that regard it is significant that in arteries of successfully aging species, the same stressors elicit a lower level of mitochondrial oxidative stress than in blood vessels of shorter-lived species, suggesting a possible link between Nrf2-dependent mechanisms regulating cellular oxidative stress resistance and slower rate of aging in longer-living species.

**Dysregulation of Mitochondrial Turnover**

Because macromolecules in mitochondria (including the mitochondrial DNA) are particularly susceptible to oxidative damage, effective control of mitochondrial turnover is critical for the maintenance of a healthy mitochondrial phenotype, normal energy production, and the promotion of healthy aging. Mitochondria are highly dynamic organelles, and dysregulation of mitochondrial turnover is likely one of the intrinsic causes of mitochondrial dysfunction, which contributes to dysregulation of cell metabolism, oxidative stress, and altered signal transduction during the aging process.

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**Table 2. Continued**

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<th>Description</th>
<th>Aging Phenotypes</th>
<th>Cardiovascular Phenotypes</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resveratrol</td>
<td>Pharmacological activator of SIRT1 and Nrf2.</td>
<td>Ameliorate shortened lifespan and metabolic derangement in aged mice fed with high-fat diet.</td>
<td>Promotes mitochondrial biogenesis, attenuates mitochondrial oxidative stress, and improves cardiac and vascular function in aged rodents or in rodent models of type 2 diabetes; protect against cardiac ischemia–reperfusion injury; attenuate atherosclerosis.</td>
<td>31, 42, 120, 122, 123, 151–154</td>
</tr>
<tr>
<td>SRT1720</td>
<td>Pharmacological activator of SIRT1.</td>
<td>Ameliorate shortened lifespan and metabolic derangement in mice fed with high-fat diet.</td>
<td>Reduce ischemic damage in heart of high-fat-diet-fed mice; attenuates atherosclerosis in LDLR−/− mice.</td>
<td>126 (also Price N, Ungvari Z, and Sinclair D, unpublished data, 2010)</td>
</tr>
<tr>
<td>Metformin</td>
<td>AMPK activator.</td>
<td>Improve aging-related cardiomyocyte dysfunction, no effect on lifespan.</td>
<td>Ameliorate cardiac ischemia, myocardial infarction, diabetic cardiomyopathy, and various animal models of heart failure.</td>
<td>131–137</td>
</tr>
<tr>
<td>MitoQ</td>
<td>Ubiquinone (antioxidant) conjugated with TPP+.</td>
<td></td>
<td>Reduce blood pressure and cardiac hypertrophy in spontaneous hypertensive rats.</td>
<td>99</td>
</tr>
<tr>
<td>SS-31</td>
<td>Tetrapeptide antioxidant targeted to mitochondria.</td>
<td></td>
<td>Attenuate angiotensin II induced cardiac hypertrophy and Gαq overexpression induced heart failure; reduce myocardial infarction.</td>
<td>100, 106</td>
</tr>
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</table>

ROS, reactive oxygen species; LV, left ventricle; mCAT, catalase targeted to the mitochondria; Polg, polymerase gamma.
mtDNA copy number concomitant with significant upregulation of the peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) and its downstream effectors, mitochondrial transcription factor A (TFAM) and nuclear respiratory factors.68 It is thought that increased mitochondrial biogenesis in the aged heart represents a compensatory maladaptive response in response to energy (ATP) deficiency, which is also stimulated by age-related oxidative damage to mitochondria.68 In contrast, aging is associated with impaired mitochondrial biogenesis and reduced mitochondrial mass in the vascular endothelial and smooth muscle cells.40,69,70 The available evidence suggests that in the aged vasculature, because of an increased production of ROS and downregulation and uncoupling of eNOS, the bioavailability of nitric oxide is significantly decreased,41 which results in a downregulation of PGC-1α and consequential dysregulation of constituents of the electron transport chain and other mitochondrial proteins.40 It is likely that decreased NO bioavailability is causally linked to dysfunction of mitochondrial biogenesis in other organs as well during aging.64,71

Mitochondria as Signaling Organelles in Aging

The original formulation of the mitochondrial theory of aging3 postulates that increased production of mitochondria-derived ROS results in a variety of macromolecular oxidative modifications, which are a primary causal factor in the aging process as well as in development of age-related diseases. In the past decade, cellular signaling events originating in mitochondria have moved into the spotlight in aging research. Mitochondrial retrograde signaling is a pathway of communication from mitochondria to the nucleus, which involves multiple factors that sense and transmit mitochondrial signals to alter nuclear gene expression. This cross-talk between mitochondria and the nucleus influences many cellular functions and is believed to play an important role in the aging process. There are multiple signaling cascades that involve the mitochondria, including release of ROS from the mitochondria, Ca2+ signaling, which activate downstream effectors pathways and transcription factors and the nutrient sensing mTOR pathway that regulates growth and cellular metabolism. Recent studies suggest that longevity is regulated by both cell-autonomous and nonautonomous mitochondrial stress pathways triggered by mild mitochondrial impairment.72 According to this model, adaptive mitochondrial retrograde pathways relay mitochondrial stress signals to the nucleus, activating genes involved in maintenance of mitochondrial integrity and cellular function. The cross-talk between the aforementioned pathways and cellular redox signaling mechanisms in the aging cardiovascular system is an important area of ongoing research.73 Here we review some of the recent advances on the signaling role of mitochondria-derived ROS in age-related pathophysiological alterations of the heart and the vasculature.

Role of Mitochondrial Signaling in Cardiac Pathophysiology in Aging

As discussed above, both RAAS activation and mitochondrial ROS play a central role in the pathophysiology of cardiac aging. Chronic administration of angiotensin II via subcutaneous osmotic pump in mice results in left ventricular hypertrophy, diastolic dysfunction, and cardiac fibrosis, all of which closely recapitulate the phenotypes of cardiac aging. Studies from Rabinovitch’s laboratory demonstrated that angiotensin II for 4 weeks increased cardiac mitochondrial DNA deletion frequency as well as mitochondrial protein carbonyls,27 both of which are related to oxidative damage to mitochondria. Angiotensin II–induced mitochondrial damage also activated mitochondrial autophagy. As a homeostatic mechanism, ROS-induced mitochondrial damage and turnover could induce signaling for mitochondrial biogenesis through activation of PGC-1α and its target genes.27 This is consistent with previous report that PGC-1α is transcriptionally upregulated by ROS.74

The critical role of mitochondrial ROS in angiotensin II–induced cardiomyopathy is reinforced by the observation that mice overexpressing catalase targeted to mitochondria (mCAT), but not mice overexpressing peroxisomal catalase (pCAT, natural site of catalase), are resistant to cardiac hypertrophy, fibrosis, and diastolic dysfunction induced by angiotensin II as well as systolic heart failure induced by cardiac-specific overexpression of Gqα (the q subunit of guanine nucleotide-binding protein).27 As shown in Figure 1, angiotensin II binds to ATR1, a Gqα protein-coupled receptor (GPCR), then activates NADPH oxidase (NOX2) via a protein kinase C-dependent mechanism.75 ROS produced by NADPH oxidase (NOX2, NOX4, or both) might increase mitochondrial ROS production in endothelial, vascular smooth muscle cells as well as neonatal cardiomyocytes.76,77 The fact that mCAT but not pCAT attenuates angiotensin II– and Gqα–induced cardiac hypertrophy and failure emphasize the central role of ROS amplification within mitochondria.27 Mechanisms of ROS amplification might include ROS-induced ROS release as well as a ROS–mtDNA damage vicious cycle (Figure 1). ROS production from NOX2/p47 phox at the cell membrane, and more specifically, NOX4 at the mitochondrial membrane (see below), could lead to electron leakage from the electron transports chain, which might further stimulate ROS production. The involvement of mitochondrial DNA mutations/deletions in this vicious cycle is supported by the observation that primary damage to mtDNA in PolgΔ/Δ mice is sufficient to increase mitochondrial ROS and induce cardiac hypertrophy and systolic dysfunction.16,27 Thus, breaking the ROS vicious cycle within mitochondria by mCAT or mitochondrial targeted antioxidants (see below) is effective to attenuate both cardiac hypertrophy and failure.

Emerging evidence has shown that NOX4 is localized to the mitochondrial membrane.78 Angiotensin II induces up-regulation of NOX4 and contributes ROS to the mitochondria, which might simultaneously consume NADPH.79,80 Detoxification of hydrogen peroxide generated by dismutation of superoxide is normally performed in mitochondria by Peroxiredoxin-3 (Prx-3) and Glutathione peroxidase (GPx). After their oxidation by hydrogen peroxide these enzymes are regenerated using the ultimate reductive power of NADPH. However, the consumption of NADPH by NOX4 establishes another potential mitochondrial vicious cycle (Figure 1). Note
that mitochondrial-targeted catalase or other mitochondrial antioxidants (see below) can break the vicious cycle by removing hydrogen peroxide or superoxide without consuming glutathione or NADPH. NADPH can itself be regenerated from NADP+ by electron exchange with NADH, catalyzed by nicotinamide nucleotide transferase (Nnt). Thus, cardiomyocyte mitochondrial redox status is intimately bound with nicotinamide adenine dinucleotide metabolism. This further implicates sirtuins (sensors of the ratio of NAD+/NADH), particularly SIRT3, in the cardiac response to stress (see below).

Recently, it has been reported that mitochondrial nitric oxide synthase (mtNOS) is also activated by angiotensin II subsequent to binding of angiotensin II to a AT2R receptor located in the mitochondrial inner membrane (mtAT2R). The mtNOS uses NADPH and arginine as substrates to generate the nitric oxide radical (NO·). NO· has been shown to regulate oxygen consumption by inhibition of cytochrome oxidase, complex IV of the electron transport chain. Thus, while consuming NADPH, production of NO could compromise respiratory function (Figure 1). In addition, formation of peroxynitrite by reaction of NO with O2− leads to increased nitrosative stress in the mitochondrial compartment (Figure 1), including damage to respiratory complexes and opening of the MPTP. However, Abadir et al noted that mtAT2R is decreased and mtAT1R density is increased in density with aging, and they speculated that activation of mtNOS by mtAT2R could be a cardioprotective mechanism. Thus, additional study is needed to determine in which circumstances this novel mechanism is protective and in which it is pathological.

**Role of Mitochondrial Signaling in Vascular Inflammation in Aging**

Inflammatory processes, particularly those mediating chronic inflammation, are known to contribute to the development of age-related cardiovascular disease, heart failure, stroke, peripheral artery disease, and vascular cognitive impairment. However, the underlying biology of aging-induced inflammation in the cardiovascular system is not completely understood. Age-related proinflammatory alterations in endothelial phenotype, known as endothelial activation, involve upregulation of cellular adhesion molecules, an increase in endothelial–leukocyte interactions, and alterations in the secretion of autocrine/paracrine mediators, which are pivotal to inflammatory responses. Previous studies both in humans and animal models of aging have demonstrated that advanced age per se alters cytokine expression profiles and promote the expression of proinflammatory genes in the wall of the large arteries, in the perivascular adipose tissue, in the microcirculation, and in the cardiac muscle as well. There is increasing evidence that activation of the redox-sensitive transcription factor NF-κB plays a key role in endothelial activation and vascular inflammatory changes in aging in humans, nonhuman primates, and laboratory rodents.

Studies continue to support a role for mitochondria-derived peptides in chronic low-grade inflammation, including NF-κB activation, which is associated with aging in the cardiovascular system. The current view is that O2−, overproduced in the aged mitochondria, is dismutated to H2O2 by Mn-SOD, and it is the increased release of H2O2 that activates NF-κB in the cytoplasm (O2− is membrane-impermeable, whereas H2O2 easily penetrates the mitochondrial membranes). Recent studies suggest that aging is associated with impairment of endogenous Nrf2-driven antioxidant defense mechanisms that protect the cardiovascular system against sustained oxidative stress and that diminished Nrf2/ARE activity in aged vessels contributes to increased mitochondrial oxidative stress exacerbating NF-κB activation in the vasculature. Further support for the link between oxidative stress and vascular inflammation in aging comes from the findings that pharmacological scavenging of mitochondria-derived H2O2 inhibits NF-κB activation in aged arteries. Overexpression of human catalase in the mitochondria of aging mice delays cardiac pathology and attenuates age-related oxidative stress and inflammation. Future studies should elucidate whether in mCAT mice, attenuation of mitochondrial H2O2 production in the endothelial and smooth muscle cells also prevents low-grade vascular inflammation associated with aging.

Recent studies also point to a new and potentially important function of mitochondrial in vascular aging: production of cytoprotective factors. Among them, the best characterized is humanin, a mitochondria-derived peptide expressed from an open reading frame within the mitochondrial 16S ribosomal RNA. It was first described as a rescue factor against neuronal cell death associated with Alzheimer’s disease, but subsequent studies demonstrated its expression in vascular endothelial and smooth muscle cells as well. Importantly, humanin was shown to confer endothelial protection inhibiting apoptosis and preventing progression of atherosclerotic plaque development in mouse models of accelerated vascular aging. Expression of humanin declines with age both in humans and mice. Thus, future studies are warranted to determine whether overexpression of humanin or treatment with humanin analogs confer vasoprotection in aging, inhibiting endothelial apoptosis or attenuating vascular inflammation. There are other small humanin-like mitochondria-derived peptides, which are known to confer prosurvival cellular effects. Future studies should characterize age-related changes in the expression profile of these peptides in the cardiovascular system and determine their role in vasoprotection. Recent studies in C. elegans show that perturbing mitochondrial function in a subset of cells sends systemic signals, termed mitokines, governing stress resistance and longevity of the entire organism. Future studies should test the possibility that modulation of the mitochondrial electron transport chain in mammalian cardiovascular cells by circulating dietary factors or pharmacological agents may also result in the secretion of diffusible mediators, which would regulate stress response pathways and inflammatory processes.

**Therapeutic Strategies to Improve Mitochondrial Function in Aging**

Pathways that improve mitochondrial function, attenuate mitochondrial oxidative stress, and regulate mitochondrial biogenesis have recently emerged as potential therapeutic...
targets for prevention of the development of age-related cardiovascular diseases (Figure 2, Table 2).

**Mitochondrial-Targeted Antioxidants**

As meta-analyses of clinical studies applying nontargeted antioxidants have shown disappointing results,92 several specific mitochondrial-targeted antioxidants have been developed. Although the experiments in rodents have been quite promising, their efficacy in attenuating mitochondrial oxidative stress in cardiovascular aging and inhibiting vascular inflammation remains as yet to be established.

**TPP**\(^+\) **Conjugated Antioxidants**

Triphenylphosphonium ion (TPP\(^+\)) has been successfully used to deliver several lipophylic antioxidants to the mitochondrial matrix, including Mito-Q (coenzyme Q), mitovitamin E, and mitophenyltertbutyline as well as SkQ1 (plastoquinone). These mitochondrial-targeted drugs can achieve concentrations in the mitochondrial matrix 100- to 1000-fold higher than those in the cytosol because of their strong positive charge, as mitochondria have a highly negative membrane potential (approximately \(-150\) mV). Mito-Q pretreatment has been shown effective in reducing ischemia–reperfusion injury in the isolated perfused hearts. Likewise, SkQ1 has also been shown to reduce infarct size in rodent model of coronary artery ligation. A recent study in spontaneous hypertensive rats demonstrated that MitoQ treatment for 8 weeks significantly reduced systolic blood pressure and reduced cardiac mass.\(^93\) The blood pressure lowering effect might be explained by the improved bioavailability of endothelial nitric oxide. The efficacy of MitoQ to reduce blood pressure provides proof of concept that mitochondria-targeted antioxidants may confer vasoprotection in aging as well. Furthermore, oral supplementation with the mitochondrial antioxidants α-lipoic acid and coenzyme Q10 reduced apoptosis in the cochlea aged mice,\(^94\) and a similar treatment paradigm was shown to improve endothelial function in the aged aorta.\(^95\)

**SS-Peptides**

The Szeto-Schiller (SS) compounds are tetrapeptides with an alternating aromatic–cationic amino acids motif, and demonstrated to concentrate in the inner mitochondrial membrane more than 1000-fold in comparison with the cytosolic concentration.\(^96\)–\(^98\) Although the positive charge might explain the mitochondrial-targeting effect, the mitochondrial uptake of these SS peptides appears to be independent on mitochondrial potential, as they are concentrated even in depolarized mitochondria.\(^96\),\(^97\) SS-31 (H-D-Arg-Dmt-Lys-Phe-NH\(_2\)) contains dimethyl tyrosine moieties, which is similar to (but even more effective than) tyrosine in having intrinsic oxygen free radical scavenging activity.\(^99\) SS-31 is able to scavenge H\(_2\)O\(_2\), hydroxyl radical, and peroxynitrite in vitro in a dose-dependent manner.\(^96\),\(^100\) SS-31 has been shown to reduce ischemia–reperfusion injury and reperfusion arrhythmia and better preserve myocardial function in various infarct models.\(^100\),\(^101\) Furthermore, it has also been shown to attenuate several age-related diseases, including Parkinson’s disease,\(^102\) Alzheimer’s disease,\(^103\) muscle weakness,\(^104\) heart failure,\(^27\) and insulin resistance.\(^105\) Studies from the Rabinovitch laboratory demonstrated that SS-31 ameliorates angiotensin II–induced cardiac hypertrophy and Gq-overexpression-induced heart failure, despite the absence of a blood pressure lowering effect.\(^106\)

Thus, preclinical studies have shown promise for both TPP\(^+\)-conjugated antioxidants and SS-Peptides in prevention...
of cardiovascular diseases. Early-phase clinical studies are ongoing, and although these are generally designed to address the efficacy of these agents in treatment of acute cardiovascular disease, it will eventually be important to also establish whether they can delay aging in the cardiovascular system.

**Calorie Restriction**

An increasing amount of data suggest that the calorie restriction confers cardiovascular protection in aging and in pathological conditions associated with accelerated cardiac and vascular aging (recently reviewed elsewhere). The mechanisms underlying the beneficial cardiovascular effects of calorie restriction are multifaceted, and include normalization of mitochondrial biogenesis, attenuation of mitochondrial ROS production, and consequent inhibition of signaling pathways regulated by mitochondria-derived ROS (e.g., NF-κB). The cellular pathways involved in mitochondrial protection induced by calorie restriction appear to depend on an increased expression/activity of the NAD+/NADH-dependent histone deacetylase SIRT1 and activation of its downstream effectors, including PGC-1α. Expression of SIRT1 in mice confer vasoprotection, reducing endothelial ROS production, inhibiting NF-κB signaling, and attenuating vascular inflammation, mimicking the effects of calorie restriction. These effects mediated by SIRT1 are likely potentiated by an increased bioavailability of nitric oxide and increased levels of adiponectin. Calorie restriction can also activate the transcription factor Nrf2, which controls the expression of numerous ROS detoxifying and antioxidant genes involved in regulation of mitochondrial redox homeostasis. Interestingly, in the heart of Nrf2 knockout mice, calorie restriction–mediated changes in SIRT1 expression are attenuated (Ungvari, Csiszar, and de Cabo, unpublished observations), suggesting that a cross-talk exists between Nrf2 and SIRT1 signaling. Recent studies suggest that in addition to SIRT1 (a nuclear enzyme), activation of mitochondrial SIRT3 may also contribute to the mitochondrial protective effects of calorie restriction. In this context it is significant that SIRT3 knockout mice show accelerated signs of cardiac aging, including reduced ATP levels.

**SIRT1 Activators and Other Calorie Restriction Mimetics**

Recent studies focus on the development of calorie restriction mimetics, to identify compounds that mimic the effects of calorie restriction by targeting cellular metabolic and stress response pathways without actually restricting calorie intake. The polyphenol resveratrol is one the first compounds, which was shown to mimic the cardiovascular protective effects of calorie restriction, including induction of mitochondrial biogenesis and attenuation of mitochondrial oxidative stress in vascular endothelial cells and in cardiomyocytes. The effects of resveratrol, in part, are attributed to its ability to upregulate or activate SIRT1, which deacetylates and activates PGC-1α and other regulators of mitochondrial function. In addition, resveratrol can also activate Nrf2 in the endothelial cells, which may also contribute to its mitochondrial protective effects.

Synthetic activators of SIRT1, such as SRT1720, were also reported to exert mitochondrial protective effects and to induce mitochondrial biogenesis in vitro. In vivo treatment with SRT1720 was recently shown to affect mitochondrial respiration in a SIRT1- and PGC-1α-dependent manner and to extend lifespan of mice fed a high-fat diet. Importantly, SRT1720 treatment in high-fat-diet-fed mice significantly reduced the number of ischemic foci in the heart and attenuated inflammatory gene expression both in the heart and in the liver. Further studies are definitely warranted to test whether mitochondrial protective effects of SRT1720 and related compounds are associated with functional improvement in the cardiovascular system of aged animals fed a standard diet.

The AMP-activated protein kinase (AMPK) has emerged as a key nutrient sensor, which acts as a master regulator of mitochondrial biogenesis, turnover, mitochondrial metabolism, and mitochondrial antioxidant defenses. There is increasing evidence suggesting that AMPK upregulates SIRT1 activity and that AMPK activation may contribute to the cardioprotective effects of calorie restriction. Because polyphenols can activate AMPK, this effect may contribute to the robust increases in cellular SIRT1 activity and other calorie restriction-like effects in vascular cells observed on resveratrol treatment. The AMPK activator metformin has been shown to ameliorate cardiac ischemia, myocardial infarction, diabetic cardiomyopathy, and various animal models of heart failure. Furthermore, it has also been shown to improve aging-related cardiomyocyte dysfunction, despite the absence of any beneficial effect on lifespan, and improve endothelial vasodilation in rodent models of accelerated vascular aging. Further studies are warranted to determine whether metformin treatment also confer mitochondrial protective effects promoting cardiovascular health in aged humans.

**Exercise**

Population-based studies clearly show that regular physical activity can reduce the risk of cardiovascular diseases, and it is assumed that some of the beneficial effects of exercise are due to its effect on mitochondrial function. The available evidence in experimental animals suggests that long-term voluntary exercise reduces mitochondrial ROS production in the heart of old rats. As mentioned above, a recent study on mitochondrial mutator (Polg<sup>−/−</sup>) mice also shows that 5 months of endurance exercise induces mitochondrial biogenesis, prevents mtDNA depletion and mutations, increases mitochondrial oxidative capacity and respiratory chain assembly, restores mitochondrial morphology, and blunts pathological levels of apoptosis in multiple tissues, including the heart, of this model of premature aging. The potential mechanisms underlying the mitochondrial effects of exercise are likely multifaceted and may include an increased shear stress–induced NO production, altered metabolism, and neurohormonal effects. A recent study demonstrated that 9 sedentary individuals older than 65 years of age prescribed a year of progressive and vigorous exercise training failed to improved age-dependent cardiac stiffening and diastolic dysfunction. However, it reduced arterial elastance and improved
maximal aerobic exercise capacity.140 Further clinical studies are needed to determine whether mitochondrial rejuvenation through exercise is an effective therapeutic approach to mitigate cardiac and vascular mitochondrial dysfunction associated with “healthy” aging in humans as well.

Other Potential Therapeutic Strategies

As discussed above, genetic disruption of AC5 is protective against cardiac hypertrophy, apoptosis, and cardiac failure by chronic catecholamine stimulation.50,51 Earlier experiments from the same group reported that direct inhibition of AC5×1R,AR-3-(6-aminopurin-9-yl)-cyclopentanecarboxylic acid hydroxyamide prevent isoproterenol-induced apoptosis in isolated neonatal cardiomyocytes.141 Further in vivo experiments using various inhibitors of AC5 are needed to elucidate the clinical potential of AC5 inhibition.

Perspectives

The important role of mitochondrial oxidative stress and mitochondrial dysfunction in age-related cardiovascular pathologies is evident, and we are at the beginning of an exciting phase of research on understanding the genetic and epigenetic mechanisms underlying the mitochondrial alterations that occur with age. Importantly, a consensus should be reached as to whether mitochondrial contributions to cardiovascular aging occur primarily via increased macromolecular damage induced by mitochondria-derived ROS or whether other mechanisms by which mitochondrial ROS and signaling affect the cellular aging process play an equally important role. The role of neurohormonal changes in age-related mitochondrial alterations needs to be elucidated further. Further research is also needed to investigate mitochondrial fusion/fission, the homeostasis of mitochondrial damage, and turnover as well as the role of cellular energetic changes, and to elucidate the precise connections between mitochondrial ROS production and mitochondrial retrograde signaling in the context of cardiovascular aging and deciphering the relationships between these processes. Future studies also should continue elucidating the cross-talk between mitochondria-derived ROS and increased activity of cell membrane-associated and cytoplasmic oxidases, including NADPH oxidases.

Mitochondria-targeted antioxidants show efficacy in various animal models, and the existing preliminary clinical data show promising results in humans. Therefore, it is likely that novel classes of mitochondria-targeted antioxidants will be developed to improve mitochondrial function promoting cardiovascular health in the elderly in various human diseases. It will be particularly interesting to test the efficacy of these novel compounds for cardiovascular indications in animal models of aging. Because age-related changes in mitochondria are likely organ specific, it is evident that much future work is required to improve the specificity of the biodistribution and penetration of antioxidant molecules delivered to mitochondria in vivo. In addition to targeting antioxidant compounds to the mitochondria, interventions that upregulate intrinsic antioxidant systems in the mitochondria can be exploited for therapeutic advantage. In particular, pharmacological or nutritional modulation of evolutionarily conserved, Nrf2/ARE-driven, or sirtuin-dependent prosurvival pathways may be effective in restoring a youthful mitochondrial function in the aged cardiovascular system, delaying the onset of age-related cardiovascular diseases. Interventions that modulate processes involved in regulation of mitochondrial turnover are also of particular interest. Finally, a deeper understanding of the mitochondria-derived signals that activate inflammatory processes may also yield new therapies for the prevention of cardiovascular diseases.

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Disclosures

None.

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