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Review

Mitochondrial regulation of cardiac aging☆

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ABSTRACT

Aging is associated with progressive decline in cardiac structure and function. Accumulating evidence in model organisms and humans links cardiac aging to mitochondrial regulation, encompassing a complex interplay of mitochondrial morphology, mitochondrial ROS, mitochondrial DNA mutations, mitochondrial unfolded protein response, nicotinamide adenine dinucleotide levels and sirtuins, as well as mitophagy. This review summarizes the recent discoveries on the mitochondrial regulation of cardiac aging and the possible molecular mechanisms underlying the anti-aging effects, as well as the potential interventions that alleviate aging-related cardiac diseases and attenuate cardiac aging via the regulation of mitochondria.

1. Introduction

Aging is commonly defined as the functional decline over time in living organisms [1]. The incidence of cardiovascular diseases dramatically increases with age. Over time, heart and vasculature gradually become homeostatic imbalance; left ventricular wall thickening and vascular stiffening and fibrosis lead to accentuated tissue adaptations and decreased stress tolerance [2]. Increased cardiomyocyte death, proliferation of myocyte nuclei, increased cardiomyocyte volume, and accumulation of connective tissues often manifest in the myocardium of old animals [3]. Continuous efforts have been made to delineate underlying mechanisms and to seek therapeutic interventions for aging-related cardiac dysfunction. Emerging from these studies, mitochondria have been demonstrated a central role in age-related pathological alterations of the heart [1,4–6].

Mitochondria play important roles in a myriad of cellular processes including ATP production via oxidative phosphorylation, fatty acid oxidation, biosynthetic pathways, urea cycle, cellular redox homeostasis, ion homeostasis, oxygen sensing, calcium storage, and regulation of programmed cell death [7]. Because more than 90% of the large amount of ATP consumed by the homeostatic maintenance and contractile function of the heart are provided by mitochondria, the heart is particularly vulnerable to mitochondrial dysfunction [8,9]. Cardiac aging is often accompanied by a general decline in mitochondrial function, clonal expansion of dysfunctional mitochondria, increased production of reactive oxygen species (ROS), suppressed mitophagy, and dysregulation of mitochondrial quality control processes [10–12]. Accordingly, development of novel therapeutic approaches for the attenuation of mitochondrial insults and rejuvenation of mitochondrial collective holds promise for decreasing morbidity and mortality related to cardiac aging.

In this review, we provide an overview of mitochondrial regulation of cardiac aging, including changes in mitochondrial morphology, mitochondrial ROS, mitochondrial DNA mutations, mitochondrial unfolded protein response, nicotinamide adenine dinucleotide levels and sirtuins, and mitophagy with age. We also discuss the major mitochondrial-related interventions against cardiac aging.

2. Cardiac aging and mitochondria

Cardiomyocytes are considered long-lived postmitotic cells that can be as old as the whole organism; thus they have a poor regeneration capacity and rare malignant transformation [13]. In human, each heartbeat consumes ~300 mg of ATP. Every day, the heart beats an average of 100,800 times, which costs ~30 kg of ATP [14]. To produce this large amount of ATP throughout life, the heart is the most mitochondrial-rich organ, densely loaded with mitochondria accounting for ~35% of the ventricular cardiomyocyte volume [15]. Mitochondria are not only the primary source of energy in the form of ATP in the heart but also act as key regulators of cardiomyocyte survival and death

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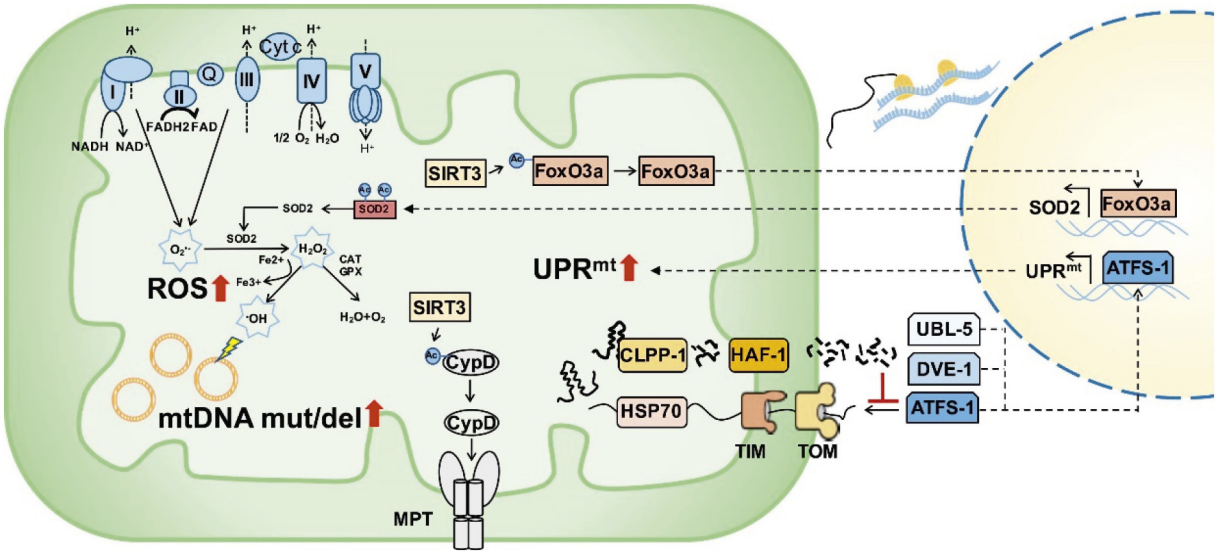

Fig. 1. Mitochondrial regulation in cardiac aging.
Superoxide ($O_2\cdot^-$) is mainly released from Complex I and III of the electron transport chain (ETC) to mitochondrial matrix or intermembrane space, respectively. $O_2\cdot^-$ can be converted to hydrogen peroxide (H_2O_2) by superoxide dismutase-2 (SOD2) inside the mitochondria. The resultant H_2O_2 is catalyzed into H_2O and O_2 by antioxidant enzymes such as catalase (CAT) or glutathione peroxidase (GPX). H_2O_2 can also be converted into the highly reactive hydroxyl radical (·OH·). Mitochondrial DNA (mtDNA) is circular, about 16.6 kb. Mitochondrial DNA mutations and deletions increase with age. SIRT3 regulates the mitochondrial permeability transition pore (mPTP) opening via the deacetylation of cyclophilin D (CypD); it also indirectly deacetylates SOD2 via the deacetylation of FoxO3a, leading to transcriptional upregulation of mitochondrial SOD2 and catalase. Mitochondrial unfolded protein response (UPR^{mt}) allays proteostatic stress in mitochondria by promoting folding, limiting import, and reducing translation of mitochondrial proteins. When an efflux of degraded peptides through HAF-1 and CLPP-1 prevents mitochondrial import of ATFS-1, it enters the nucleus along with homeobox transcription factor (DVE-1) and ubiquitin-like protein (UBL-5) and activate UPR^{mt}.

[16]. Impaired mitochondrial function is often implicated in and contributes to cardiac aging and related diseases [16].

Major theories of aging include the free radical theory [17], immunologic theory [18], inflammation theory [19], all attributing aging to a particular cause. Among these different theories, the free radical theory, especially the mitochondrial free radical theory claiming that biological aging is caused by ROS production and subsequent damage, has been the major focus of the studies on aging [17]. Later, the revised mitochondrial free radical theory attributes the failures of antioxidants to extend lifespan in animal experiments and clinical trials to the possible poor distribution of antioxidants to mitochondria and proposes that mitochondrial-targeted antioxidants might be beneficial for lifespan extension [20]. Another mitochondrial theory of cellular aging is based on the fact that mitochondrial DNA (mtDNA) has a high rate of mutation but limited repair capacity [21]. Accordingly, mtDNA mutations accumulate with age and compromise the integrity of mitochondrial genome [21]. Consequently, mitochondrial function is impaired and their ability to produce energy is gradually lost while more ROS are generated [22]. Over time, dysfunctional mitochondria accumulate and result in energy shortage along with growing oxidative burden that leads to cellular damage or even death. In this theory, mtDNA mutation rates are considered as the “aging clock” that initiates aging events that determine the overall organism longevity [16]. Despite of the debates among the major theories of aging, mitochondrial integrity is undoubtedly of vital importance for cardiac homeostasis during aging.

2.1. Mitochondrial morphological changes in cardiac aging

Mitochondria are double-membrane organelles in most eukaryotic organisms, comprising the outer (OMM) and inner membranes (IMM), intermembrane space (IMS), and cristae formed by the extensive invagination of the IMM [23]. The inner membranes of mitochondria harbor the electron transport chain (ETC) that produces ATP through oxidative phosphorylation (OXPHOS) [24]. Other energy-producing processes including fatty acid oxidation and tricarboxylic acid cycle also take place in mitochondria [25].

Mitochondria are “already fragmented” and “seemingly static” individual rods in the heart, opposite to those seen in many other organs. Cardiac mitochondria often exist in two functionally distinct populations. Subsarcolemmal mitochondria (SSM) are situated beneath the sarcolemma, whereas interfibrillar mitochondria (IFM) reside between the myofibrils [26]. SSM possess largely lamelliform cristae, whereas mitochondrial cristae in IFM display mostly tubular morphology [27]. Morphometric studies show that the density of mitochondrial cristae, the size of individual mitochondrion, and the number of mitochondria per cell often change with age [28]. In Wistar rats, mitochondrial volume is decreased in both left and right ventricles of the 2-year group when compared to that of the 6-week group. Mean size of mitochondria is decreased by 36% and 11% in the left and right ventricles, respectively. The density of mitochondrial cristae is also markedly decreased, evidenced by the loss of strict parallel position [29]. In OXYS rats, a unique model for studying the role of oxidative stress in age-related pathologies, cardiomyocyte mitochondrial ultrastructure degenerates earlier than do the age-matched controls [28]. However, there are also reports showing no mitochondrial cristae degeneration with age [30]. In rats where both protein yield and oxidative phosphorylation rate are decreased specifically in aged cardiac IFM rather than SSM, ultrastructural analyses of the in situ and isolated cardiomyocyte mitochondria failed to disclose any age-related changes in the configuration of the mitochondrial cristae in either IFM or SSM [30,31].

2.2. Cardiac aging and ROS

ROS are reactive (oxidizing) chemical species containing oxygen, ranging from highly reactive hydroxyl group to longer-lived membrane-permeant hydrogen peroxide. The major sources of ROS in intact cardiomyocytes are usually mitochondrial OXPHOS Complex I and III [32]. Superoxide (O_2^-) is formed by electrons binding to diatomic oxygen (O_2) in Complex I and III and is released into the mitochondrial matrix and intermembrane space, respectively [33]. About 2% of O_2 in the mitochondria ends up O_2^-, which can be converted to hydrogen peroxide (H_2O_2) by superoxide dismutase-2 (SOD2) inside the

mitochondria. The resultant H_2O_2 is then catalyzed into H_2O and O_2 by antioxidant enzymes such as catalase or glutathione peroxidase. Notably, H_2O_2 can also be converted into the highly reactive hydroxyl radical (·OH) through Fenton and Haber-Weiss reactions in the presence of iron [34] (Fig. 1).

Direct evidence for mitochondrial ROS driving cardiac aging is provided by the experiments in which mice overexpressing mitochondrial-targeted catalase (mCAT) exhibit an 18% prolongation of lifespan, whereas mice overexpressing peroxisomal (pCAT) or nuclear-localized (nCAT) catalase do not [35]. The overexpression of mCAT alleviates phenotypes caused by age-dependent mitochondrial oxidative stress, as evidenced by significant reduction of mtDNA mutations, decreased mitochondrial protein carbonyls, better preservation of mitochondrial cristae, and attenuation of age-dependent activation of organelle biogenesis [36]. In the heart, the protective effects of mCAT are displayed by the reversal of age-dependent increase in left ventricular mass index, decline in contractile function and enlargement of left atrium [37]. Furthermore, in response to thrombin treatment, vascular smooth muscle cells (VSMCs) generate more ROS with higher degrees of cellular and mitochondrial oxidative damage in aged mice than in younger controls. In addition, mitochondrial expression of Nox4 that is a major intracellular isoform of nicotinamide adenine dinucleotide phosphate oxidase is also upregulated in aged hearts, further associating increased ROS production with age-related cardiac abnormalities [38]. The overexpression of the mitochondrial manganese superoxide dismutase-2 (MnSOD), however, fails to prolong lifespan in mice [39].

Despite of the detrimental effects caused by excessive mitochondrial ROS, a slight increase in mitochondrial ROS production can activate redox-sensitive pathways, resulting in long-lasting geroprotective effects. This is the so-called mitohormesis that refers to the notion that a little stress can protect against larger, subsequent stresses [40,41]. Arsenite induces a transient increase of ROS that confers mitohormesis. In cell lines and *C. elegans*, low-dose arsenite promotes cell growth and extends lifespan by enhancing resistance against thermal and chemical stressors, whereas high-dose of arsenite impairs cell growth and reduces lifespans [42]. A similar hormetic response is implicated in the mitochondrial ROS-dependent activation of HIF-1 in rescuing *C. elegans* AMPK-null mutants [43] that die prematurely of the exhaustion of triglyceride stores; increased hydrogen peroxide levels improve the survival rate of these mutants by re-adjusting their lipid biosynthetic capacity via increased expression of key enzymes involved in fatty-acid biosynthesis in a HIF-1-dependent manner [42]. In addition, ROS have been shown to induce compensatory autophagy to eliminate damaged mitochondria when PARKIN-mediated mitophagy is compromised, further demonstrating the physiological necessity of ROS in maintaining cardiac homeostasis [44].

2.3. Mitochondrial DNA (mtDNA) mutations during cardiac aging

Mitochondria are semi-autonomous in that they have their own DNA and ribosomes for making some of the mitochondrial proteins. The circular mitochondrial DNA (mtDNA) genome is about 16.6 kb, encoding 13 mitochondrial proteins that are the subunits of electron transport chain, as well as 22 tRNAs and 2 rRNAs for the transcription and translation of these proteins, respectively [45] (Fig. 1). It has been well documented that mtDNA point mutations and deletions accumulate with age in various tissues including the heart in human and rodents [46–48]. Examination of the mtDNA D-loop in 2- to 22-month mice reveals no mtDNA mutations found in young mice but in old mice, with an estimation of the mtDNA mutation frequency of old mice 1000-fold higher than that for nuclear genes [46–48]. In human, mtDNA deletions emerge in normal hearts of individuals over 40 years old and subsequently accumulate with age [46–48].

Increased mtDNA mutations promote aging [49,50]. The mutator mice with ectopic expression of a proof-reading-deficient Polγ have accumulated mtDNA mutations in multiple organs including the heart, brain and liver compared to the wildtype mice. At the age of 8 weeks, the mtDNA mutation accumulation rate in the mutator mice is already 3 to 5 times higher than those in the wildtype mice. Large deletions are detected in about 30% of the mtDNA genome [49]. By 25 weeks, the mutator mice exhibit premature aging phenotypes, including the development of osteoporosis, hair loss and reduced fertility [50]. Within the first year of life, the mutator mice develop cardiac hypertrophy and dilatation, impairment of diastolic and systolic function and cardiac fibrosis, with an average lifespan of only 48 weeks [36,50,51]. This age-dependent mtDNA mutation-induced cardiomyopathy is associated with exacerbated protein oxidative damage, increased expression of apoptotic and senescence markers, and decreased mitochondrial biogenesis [52]. These adverse phenotypes in the mutator mice can be attenuated by the overexpression of mitochondrial-targeted catalase (mCAT) [35], suggesting that the cardiomyopathy caused by accumulated mtDNA damage is partially mediated by mitochondrial oxidative stress.

2.4. Mitochondrial unfolded protein response (UPR^{mt}) and cardiac aging

Mitochondrial unfolded protein response (UPR^{mt}) was first described as the transcriptional activation of mitochondrial-specific chaperones in mitochondrial DNA-deficient rat hepatoma cells [53]. UPR^{mt} serves as a link between mitochondrial proteostasis and aging in various organisms. It relieves the proteostatic stress in mitochondria by promoting folding, limiting import, and reducing translation of mitochondrial proteins [54,55]. UPR^{mt} was initially described in mammalian cells [56], but the underlying mechanisms have been mainly investigated in *C. elegans* of which the UPR^{mt} pathways are similar to those of the mammals. Later, it was found that the imbalance between nuclear- and mitochondrial-encoded electron transport chain components activates UPR^{mt} [57,58]. Consistently, respiratory chain inhibitors such as antimycin and rotenone [59], inhibition of mitochondrial proteases, chaperones, respiratory chain complex assembly factors [60] as well as mitochondrial tRNA synthetases [61] also activates UPR^{mt}.

The relevance of UPR^{mt} to lifespan was initially established based on studies in *C. elegans* with respiratory defects [57,62] and has now been well supported by findings in multiple model organisms [63]. Reduced expression of mitochondrial ribosomal proteins activates UPR^{mt}, positively correlating with lifespan extension in *C. elegans* and mice [57]. In addition, mild mitochondrial distress in muscle preserves mitochondrial function and impedes the age-dependent deterioration of muscle function and architecture partially via the compensatory activation of UPR^{mt}, resulting in prolonged lifespan in *Drosophila* [63].

Despite of the strong association between UPR^{mt} and longevity, whether UPR^{mt} activation is necessary or sufficient for lifespan extension remains to be determined. ATFS-1 encodes the nuclear transcription factor that turns on the UPR^{mt} by sensing mitochondrial stress (Fig. 1). However, in *C. elegans*, gain-of-function ATFS-1 alleles are not able to prolong lifespan [64], and loss-of-function ATFS-1 alleles do not always prevent lifespan extension by knockdown of ETC subunits [64]. Yet, even though the ATFS-1-dependent UPR^{mt} [64] per se might not confer longevity, they seem to be necessary for lifespan extension as UPR^{mt} activation is observed in all long-lived *C. elegans* mutants with stressed mitochondria [64,65].

It has been reported that UPR^{mt} is increased in aged mouse hearts [66]. In the heart tissues of 13 mammalian and avian species the expression of Hsp60 is also positively correlated with maximum lifespan [67]. Still, studies on the role of UPR^{mt} in cardiac aging are limited. Whether UPR^{mt} as a fundamental mechanism of longevity could be applied to basic research and clinical settings against cardiac aging awaits further investigation.

2.5. Nicotinamide adenine dinucleotide (NAD^+) and cardiac aging

Nicotinamide adenine dinucleotide (NAD^+) is an electron acceptor in the mitochondrial electron transport chain. Cellular NAD^+ levels are regulated by the balance between the synthesis through de novo and salvage pathways and the consumption by sirtuins and poly(ADP-ribose) polymerase (PARP) [68].

NAD^+ salvage pathway is critical to maintain cellular NAD^+ levels via the recycle of the nicotinamide generated as a by-product of the enzymatic activities of the NAD^+-consuming enzymes. In turn, nicotinamide not only regulates the enzymatic activities of the NAD^+-consuming enzymes as an inhibitory factor by binding in a conserved NAD^+ pocket, but also is a biosynthetic precursor to NAD^+ via the activities of nicotinamide phosphoribosyltransferase (NAMPT) and nicotinamide mononucleotide adenylyltransferase (NMNAT) [68,69].

NAD^+ levels decrease with age in many organs including the heart [3]. Loss of Complex I of the electron transport chain is associated with an increase in NADH and a relative decrease in NAD^+, resulting in decreased SIRT3 activity, increased mitochondrial protein acetylation, and accelerated heart failure in response to chronic stress [68]. On the contrary, supplementation of NAD^+ via its precursors including nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR) attenuates cardiac aging via the activation of sirtuins and resultant increased cellular protein deacetylation. For example, supplementation of NMN in mice increases NAD^+ levels in cardiomyocytes and protects the heart from ischemia reperfusion injury at both ischemic and reperfusion phases, accompanied by the deacetylation of Forkhead box O1 (FOXO1)-mediated through the activation of SIRT1 [70]. After long-time ischemia NAMPT is downregulated with decreased levels of NAD^+ and autophagy, thus leading to cell death. On the opposite, NAMPT overexpression restores the levels of NAD^+ and autophagy, thus reducing the infarct size from myocardial infarction [71].

On the other hand, activated PARP rapidly consumes ADP-ribose monomers, thus depleting its precursor NAD^+ and inducing cell death [72]. In aged *C. elegans*, restoring NAD^+ with PARP inhibitors effectively prevents age-related metabolic decline and prolongs lifespan dependent upon sir2.1 (ortholog of mammalian SIRT1) [73].

2.6. Mitochondrial protein deacetylation and cardiac aging

Sirtuins (SIRTs) are a highly conserved family composing of seven mammalian NAD^+-dependent deacetylases that are first described in yeast as silent information regulators and are now known to regulate a variety of biological processes, including metabolic homeostasis, stress response and aging [74]. Mammals contain seven Sir2 homologs (SIRT1–7) that share a conserved 275-amino-acid catalytic domain [75,76]. These sirtuins are localized in different subcellular compartments, that is, the nucleus (SIRT1, 2, 6, 7), the cytoplasm (SIRT1, 2) and the mitochondria (SIRT3, 4, 5) [77]. Despite that these enzymes are generally known as lysine deacetylases that remove acetyl modifications from lysine residues [78], these sirtuins possess distinct catalytic preferences and efficiencies [73,74,79]. The mitochondrial sirtuins include SIRT3, SIRT4 and SIRT5. SIRT3 displays robust deacetylase activity; SIRT4 mainly functions as a lipoamidase and ADP-ribosyltransferase; SIRT5 mainly mediates the acidic acyl modifications including lysine succinylation, malonylation, and glutarylation [77–82].

2.6.1. SIRT1

SIRT1 is the most studied prototype member of this family. It is mainly localized in the nucleus and cytoplasm and also in the plasma membrane [83]. Several lines of evidence show that SIRT1 plays vital roles against cardiac aging and diseases. Transgenic mice with cardiac-specific SIRT1 overexpression are protected from age-related cardiac hypertrophy as well as ischemia or reperfusion injury [84,85]. In vascular endothelial cells (VECs), SIRT1 deacetylates endothelial nitric oxide synthase (eNOS), stimulating eNOS activity and thus increasing endothelial nitric oxide (NO) [86]. Upon activation by resveratrol, SIRT1 also deacetylates poly(ADP-ribose) polymerase 1 (PARP1) and inhibits PARP-mediated cell death. Consistently, SIRT1 deficiency increases PARP-mediated cardiomyocyte death during heart failure [87,88]. In addition, PARP2 has been implicated in cardiac hypertrophy. Upon PARP2 knockdown or the treatment with a small-molecule inhibitor of PARP2, alpha-lipoic acid (ALA), reactivated SIRT1 protects against cardiac hypertrophy; by comparison, SIRT1 knockdown abrogates the beneficial effects of ALA on cardiomyocyte hypertrophy [89].

2.6.2. SIRT2

SIRT2 is mainly present in the cytoplasm and also to a less extent in the nucleus. SIRT2 can act as a deacetylase for α-tubulin and FOXO1 during oligodendroglial differentiation and adipogenesis, respectively [90–92]. In the nucleus, SIRT2 regulates H4K16Ac levels and controls cell cycle. Murine embryonic fibroblasts (MEFs) with SIRT2 deficiency exhibit excessive H4K16 acetylation during mitosis, causing a delay in S-phase entry [93].

SIRT2 plays an important role in the maintenance of cardiac homeostasis. SIRT2 is downregulated during cardiac hypertrophy. SIRT2-deficient mice exaggerate cardiac hypertrophy, remodeling, fibrosis, and dysfunction in aged mice and mice infused with Angiotensin II (Ang II). On the contrary, SIRT2 overexpression attenuates Ang II-induced cardiomyocyte hypertrophy and rescues cardiac function as a deacetylase by negatively regulating NFAT transcriptional factor and activating LKB1-AMPK signaling [94]. Therefore, SIRT2 may be a potential therapeutic target for aging- and stress-induced cardiac hypertrophy [95].

2.6.3. SIRT3

SIRT3 is a major mitochondrial deacetylase primarily localized in the mitochondrial matrix (Fig. 1). SIRT3 is directly linked to longevity and highly expressed in long-lived individuals [96]. It acts as a metabolic sensor via the use of intracellular metabolites including NAD^+ and acetyl-CoA to modulate mitochondrial function to meet the energy demand of the cell [97]. SIRT3 can also regulate mitochondrial biogenesis; ectopic expression of SIRT3 in brown adipocytes increases the phosphorylation of cAMP response element binding protein (CREB), which subsequently stimulates the expression of peroxisome proliferative activated receptor gamma coactivator 1 alpha (PGC-1α) and its target gene uncoupling protein 1 (UCP1) [98,99]. In addition, SIRT3 is critical in fatty acid oxidation by positively regulating the activity of the rate-limiting ketogenic enzyme 3-hydroxy-3-methyglutaryl-CoA synthase isoform 2 (HMGCS2) via deacetylation and desuccinylation [100,101]. SIRT3 also regulates the urea cycle by deacetylation and activation of ornithine transcarbamylase (OCT); metabolomic analysis of fasted mice lacking SIRT3 revealed a clear perturbation in metabolic intermediates of urea cycle [102]. In the heart, SIRT3 functions as a direct regulator of basal ATP levels and mitochondrial electron transport. SIRT3 overexpression augments Complex I activity, whereas SIRT3 deficiency inhibits Complex I activity due to increased mitochondrial protein acetylation, resulting in a 50% decrease in basal ATP content [103].

SIRT3 plays an important role in cardiac aging. Human SIRT3 has two isoforms, a 44 kD full-length isoform (fl-SIRT3) and a 28 kD short isoform (sh-SIRT3). Sh-SIRT3 is the predominant form in young myocardial tissues whereas fl-SIRT3 is mainly expressed in the aged hearts [104]. SIRT3 protects against cardiac aging by controlling oxidative stress and suppressing cardiac hypertrophy [105]. The overexpression of SIRT3 suppresses Ang II-induced cardiac hypertrophy and fibrosis, and inhibits the expression of fibrotic markers in myofibroblasts of failing human hearts [106]. Consistently, SIRT3 levels are decreased in the fibroblasts isolated from the patients with end-stage heart failure and SIRT3 deficiency exacerbates cardiac hypertrophy and induces

interstitial fibrosis [107]. In addition, SIRT3 can attenuate HIF-1α activity indirectly by controlling intracellular ROS levels [108]. Another important pathway for the cardioprotective effects of SIRT3 is via the regulation of mitochondrial permeability transition pore (mPTP). SIRT3 deacetylates the regulatory component of the mPTP, cyclophilin D and inhibits mPTP opening in the heart, thereby reducing oxidative stress, preventing cardiomyocyte death and slowing down cardiac aging. Accordingly, SIRT3-deficient mice exhibit an age-dependent increase in cardiomyocyte mitochondrial swelling due to increased mPTP opening [109].

2.6.4. SIRT4

SIRT4 is known more as a lipoamidase and ADP-ribosyltransferase, rather than a robust deacetylase with the exception that it controls lipid catabolism via the deacetylation of malonyl-CoA decarboxylase (MCD) [75,110,111]. SIRT4 knockout does not induce mitochondrial protein hyperacetylation [110]. By comparison, as a lipoamidase, SIRT4 regulates the pyruvate dehydrogenase complex (PDH) that converts pyruvate to acetyl-CoA [79]. As an ADP-ribosyltransferase, SIRT4 inhibits the activity of glutamate dehydrogenase (GLUD1) that catalyzes the conversion of glutamate to a-ketoglutarate by ADP-ribosylation and downregulates amino acid-dependent insulin secretion [110]. SIRT4 is also implicated in the regulation of fatty acid oxidation in liver and muscle, though the underlying mechanisms remain to be elucidated [112]. In H9c2 cardiomyoblasts, SIRT4 inhibits hypoxia-induced apoptosis by suppressing mitochondrial Bax translocation through the regulation of the ratio of pro-caspase 9/caspase 9 and pro-caspase 3/caspase 3 [113]. After ischemia-reperfusion injury, SIRT4 is downregulated in cardiomyocytes and SIRT4 overexpression protects hearts by preserving mitochondrial function and reducing cardiomyocyte apoptosis in mice [114].

2.6.5. SIRT5

SIRT5 mediates the removal of succinyl, malonyl, glutaryl, rather than acetyl, groups from mitochondrial targets [82]. Consistently, SIRT5 knockout does not induce mitochondrial protein hyperacetylation, either [110]. With succinylation identified as a new relevant modification of lysine residues, SIRT5 is now emerging as a key regulator of mitochondrial proteins and metabolism [74]. SIRT5-deficient mice exhibit accumulation of acylcarnitines and decreased β-hydroxybutyrate production. In addition, SIRT5 regulates succinylation of HMGCS2 both in vivo and in vitro, further demonstrating an important role for SIRT5 in regulating β-oxidation and ketone body synthesis [101]. SIRT5 can also act as a lysine deglutarylase to regulate the activity of carbamoyl phosphate synthase 1 (CPS1) that is the rate-limiting in urea cycle [115]. In cardiomyocytes, SIRT5 is downregulated by oxidative stress and SIRT5 knockdown significantly increases ROS-induced cardiomyocyte apoptosis [116]. However, it is unknown whether SIRT5 regulates ROS in the heart [76] and also its role during ischemia reperfusion remains to be elucidated [79].

2.6.6. SIRT6

SIRT6 is mainly in the nucleus. SIRT6-knockout mice exhibit aging-like phenotypes, including profound lymphopenia, loss of subcutaneous fat, severe hypoglycemia, and eventually premature death before 4 weeks of age [117,118]. SIRT6 was first identified as an ADP-ribosyltransferase [119] and also implicated in DNA double-strand break repair by regulating C-terminal binding protein (CtBP) and DNA protein kinase [120,121]. Recent studies reveal that SIRT6 also acts as a deacetylase preferentially on lysine (K) residue 9 and 56 of histone H3 (H3K9, H3K56) [119,122,123]. By binding to the promoter regions of HIF-1α target genes and deacetylating histone H3K9, SIRT6 acts as a co-repressor of HIF-1α and transcriptionally suppresses glycolysis. SIRT6-deficient MEFs and mice exhibit increased HIF-1α activity and glycolysis but significantly decreased mitochondrial respiration, thus accounting for the severe hypoglycemia in SIRT6-knockout mice [124]. How SIRT6 regulates cardiac aging awaits further investigation.

2.6.7. SIRT7

SIRT7 is an activator of RNA polymerase I transcription [125]. SIRT7-knockout mice show various signs of aging-related changes including kyphosis, loss of subcutaneous fat, hypertrophic and inflammatory cardiomyopathy, and eventually premature death. In addition, SIRT7-deficient primary cardiomyocytes are less resistant to oxidative and genotoxic insults and increased apoptosis, indicative of a vital role of SIRT7 in regulating stress responses and cardiomyocyte death in the heart [126].

2.7. Cardiac aging and mitophagy

Autophagy is a catabolic process that degrades cytoplasmic components and organelles in response to stresses such as nutrient starvation, oxidative stress, and inflammatory stimuli. Autophagy is implicated in various physiological processes including cell survival during starvation, degradation of aggregated proteins, clearance of dysfunctional organelles, development, differentiation and aging [127,128]. Myocardial autophagy declines with age. Knockout of macrophage migration inhibitory factor (MIF) exacerbates aging-related cardiac remodeling and functional deterioration associated with accelerated loss of autophagy in the heart [129]. Conversely, aging-associated myocardial dysfunction and cardiac hypertrophy may be exacerbated upon the suppression of autophagy by mitochondrial aldehyde dehydrogenase (ALDH2) whereas AKT2 ablation protects against cardiac aging and prolongs lifespan via the restoration of FOXO1-mediated autophagy and preservation of mitochondrial integrity [130,131].

Damaged mitochondria beyond repair can be eliminated through a specialized form of autophagy termed mitophagy [132]. It is generally accepted that mitophagy also declines with age [13]. The best characterized form of mitophagy is initiated by mitochondrial serine/threonine kinase PTEN-induced putative kinase 1 (PINK1) and the cytosolic E3 ubiquitin ligase PARKIN. PINK1 is translocated onto the inner mitochondrial membrane via the translocase of the outer mitochondrial membrane (TOM) and the translocase of the inner mitochondrial membrane (TIM) complexes [132]. Under normal steady-state conditions, it is rapidly and constitutively degraded by the presenilin-associated rhomboid-like protease (PARL) [133]. When mitochondrial import through the TIM complex is disrupted by stresses including mitochondrial depolarizing agents, OXPHOS inhibitors, genetic or environmental stresses, the translocation of PINK1 onto the inner membrane where PARL resides is inhibited. Accordingly, PINK1 is preserved from PARL-mediated degradation and accumulates on the outer mitochondrial membrane [134], where it phosphorylates the outer mitochondrial membrane protein MFN2 that in turn facilitates the recruitment of cytosolic E3 ubiquitin ligase PARKIN to these mitochondria to initiate mitochondrial degradation via mitophagy [135,136] (Fig. 2).

There is a generally accepted concept that mitochondrial dysfunction may be featured in cardiac aging. In *C. elegans*, oxidative stress promotes both mitochondrial biogenesis and mitophagy through skinhead-1 (SKN-1, a homolog of NRF2), thereby coordinating mitochondrial turnover [137,138]. Young germline PARKIN knockout mice exhibit normal cardiac function, whereas abnormal mitochondria accumulate in cardiomyocytes with age [139], implying the role of PARKIN-mediated mitophagy in aging hearts. Yet, the changes in mitophagy have merely been quantified during cardiac aging [3].

The later event of macroautophagy is highly dependent on the availability of autophagy-related proteins (ATGs). Among others, ATG5 is recognized as a key player for autophagosome formation but also for inducing apoptosis. As part of the ubiquitin-like conjugation systems, ATG5 interacting with ATG12 mediates the formation of a multimeric complex localizing to the developing autophagosome membrane and is

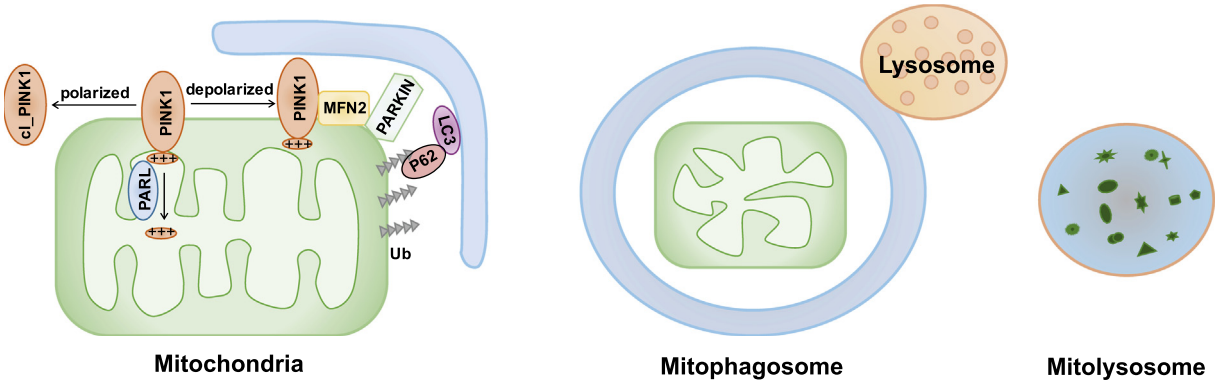

Fig. 2. Schematics of classical PINK1-MFN2-PARKIN-mediated mitophagy.
Under normal conditions (polarized mitochondria), PTEN-induced putative kinase 1 (PINK1) is translocated onto the inner mitochondrial membrane and constitutively cleaved by presenilin-associated rhomboid-like (PARL) protease, resulting in the release of cleaved PINK1 into the cytosol for degradation via the ubiquitin-proteasome system. When mitochondria are depolarized, the proton gradient driving the import of PINK1 into mitochondria disappears and PINK1 is diverted from the cleavage by PARL on the inner mitochondrial membrane. Instead, full-length PINK1 accumulates on the outer mitochondrial membrane and phosphorylates mitofusin 2 (MFN2), which subsequently recruits mitochondrial E3 ubiquitin ligase PARKIN from the cytosol to the depolarized mitochondria. PARKIN then mediates the polyubiquitination of mitochondrial outer membrane proteins including p62, leading to the recruitment of LC3 to form mitophagosome. Once formed, mitophagosome is delivered to lysosome to fuse into mitolysosome for the ultimate degradation.

dissociated from the membrane once the autophagosome is complete [140]. Mice with cardiomyocyte-specific deletion of ATG5 develop lethal dilated cardiomyopathy at the age of ten months, resulted from the accumulation of structurally deteriorated mitochondria with impaired respiratory function due to impaired mitochondrial culling [141], indicating that mitophagy is vital to preserve cardiac function in aged hearts. Ectopic expression of ATG5 in mice extends lifespan by 17% compared to non-transgenic controls [142].

Mitochondria can also be degraded via mitochondrial-derived vesicles (MDVs). In H9c2 cardiac myoblasts, MDV formation occurs under basal conditions and can also be rapidly induced in response to stress. Similarly, in mouse hearts MDVs form readily under normal steady-state conditions while mitophagy is usually more potently induced under stress [143]. Once formed, delivery of MDVs to the lysosomes is PINK1- and PARKIN-dependent [144] but does not require mitochondrial depolarization and is independent of ATG5 and LC3 [145], pointing to the differences between MDVs and canonical PINK1/PARKIN-mediated mitophagy in the integrated mitochondrial quality control machineries [146].

3. Interventions against cardiac aging

Mitochondrial-targeted strategies that limit cardiac injury can often lead to the functional improvement of aged hearts. Here we review several major interventions against cardiac aging at least partially via the regulation of mitochondria, including exercise, calorie restriction, nicotinamide riboside and derivatives, as well as senolytic drug candidates (Fig. 3).

3.1. Exercise and cardiac aging

Exercise is a diagnostic and therapeutic tool against aging-related cardiac diseases, in part via the preservation of mitochondrial integrity [147]. Four-week voluntary treadmill running in adult mice increases the mitochondrial number and left ventricle volume [148]; five-month treadmill exercise in the mutator mice induces mitochondrial biogenesis and increases mitochondrial oxidative capacity, thus protecting against cardiomyocyte apoptosis and spontaneous cardiac hypertrophy [149]. On a molecular level, endurance exercise increases PGC-1α expression and thus promotes mitochondrial biogenesis in the heart [150]. SIRT1 and SIRT3 are also upregulated in the heart during exercise and play cardioprotective roles against oxidative stress partially by FOXO3a-dependent signaling pathways that increase the levels of superoxide dismutase and catalase [107].

3.2. Calorie restriction and cardiac aging

Calorie restriction (CR) is defined as a dietary regimen that decreases calorie intake without incurring malnutrition or insufficiency in essential nutrients. CR typically consists of an energy intake that is only 50–70% of that required to maintain normal body weight [139]. CR has been shown to extend lifespan in varied organisms ranging from yeast to mice, as well as to attenuate age-related diseases such as cancer, diabetes and neurodegenerative diseases [151]. The detailed mechanisms by which CR extends lifespan have not been fully elucidated, but increasing evidence reveals that the decreases in mitochondrial ROS production, lipid peroxidation, protein oxidation and mtDNA oxidative damage may all contribute to its anti-aging effects in various organs [152–154]. In the heart, CR attenuates age-related changes including myosin isoform shifts, cardiomyocyte apoptosis, cardiac fibrosis, as well as diastolic dysfunction [155]. It has been shown that mitochondrial oxidative damage to mitochondrial DNA, proteins, and lipids can be significantly reduced by CR in the aged heart [154,156–159]. For example, the levels of 8-oxodG are lower in cardiac mitochondria isolated from long-term caloric-restricted rats than ad libitum-fed controls [156,159]. In addition, the increase in mitochondrial protein acetylation level with age in rat hearts can also be attenuated upon CR via the enhancement of mitochondrial sirtuin (SIRT3, 4, 5) activities, but not protein levels [160].

3.3. Nicotinamide riboside and cardiac aging

Mitochondrial dysfunction has been implicated in heart failure and is often accompanied with an imbalance in the intracellular ratio of reduced nicotinamide-adenine dinucleotide (NADH) to oxidized nicotinamide-adenine dinucleotide (NAD^+) [161,162]. In mice, restoration of the NADH/NAD^+ ratio through the supplementation with NAD^+ precursors significantly improves cardiac function. Nicotinamide riboside (NR) is a pyridine-nucleoside form of vitamin B3 and NAD^+ precursor. With cellular NAD^+ concentrations changing with age, supplementation of NR increases lifespan in yeasts and worms in a sir2.1-dependent manner [163] and protects against metabolic abnormalities induced by high-fat diet in mice via the activation of SIRT1 and SIRT3 and promotion of oxidative metabolism [164]. With the ongoing clinical trial (ClinicalTrials.gov Identifier: NCT03423342) focusing on the safety and tolerability of NR in patients with systolic heart failure, we

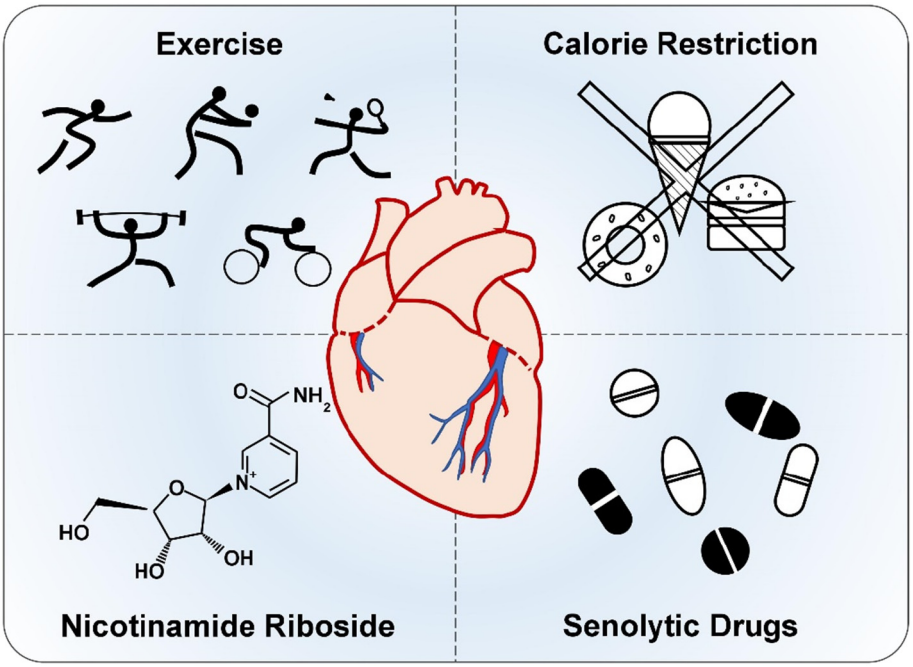

Fig. 3. Major interventions against cardiac aging.

look forward to further understanding the beneficial effects of NR as a new therapeutic opportunity for cardiac aging and related diseases.

3.4. Senolytic drug candidates against cardiac aging

Aging and aging-related diseases in part stem from the accumulation of senescent cells, which disturbs homeostasis. Senolytics are a new class of drugs with the potential to slow down the aging process via specific and efficient elimination of senescent cells. Studies in animal models have demonstrated prolonged healthspan and lifespan through the use of senolytic therapies [165]. Here, we try to provide an overview for several of the most well-studied senolytic drug candidates.

3.4.1. Resveratrol

Resveratrol is a polyphenolic flavonoid found in red wine, mulberries, peanuts, and rhubarb. This polyphenolic compound prolongs the replicative lifespan of yeast [166] and the life of worms [167] and flies [168]. In mice, resveratrol attenuates doxorubicin-mediated cardiotoxicity and left ventricular remodeling [169]. In monkeys fed with a diet high in sugar and fat, resveratrol improves vascular function [170]. Mechanistically, early targets of resveratrol are the sirtuins [171]. Resveratrol suppresses cardiac fibroblast proliferation and cardiac hypertrophy [172], in which resveratrol-activated sirtuins may stimulate AMPK pathway and improve mitochondrial and cardiac function [173,174]. In cardiac fibroblasts, resveratrol ameliorates collagen deposition and thus improves cardiac function via the activation of SIRT3 [175]. Rats administrated with Longevinex, a commercialized resveratrol formulation, also exhibit better cardiac performance, smaller cardiac infarct size and prolonged longevity via the induction of autophagy along with the upregulation of SIRT1 and SIRT3 after ischemia reperfusion injury [176]. Another target of resveratrol is Class IA phosphoinositide 3-kinase (PI3K), whose inhibition by resveratrol by competing with ATP for the catalytic site may promote longevity independent of sirtuins [177].

3.4.2. Metformin

Metformin, a biguanide first isolated from the French lilac, is the most prescribed drug for type-2 diabetes [163]. Metformin reduces oxidative stress and chronic inflammation, two of the most well-known factors that compromise health and lifespan [178]. Metformin acts partially via the inhibition of mitochondrial functions and stimulation of AMPK activity by an increase of the AMP/ATP ratio, thereby inhibiting mTOR [179]. In aged *C. elegans* and mice, metformin extends lifespan via a mitohormetic effect [180]. In diseased mouse hearts, metformin reverses pressure overload-induced cardiac fibrosis and improves cardiac diastolic function after transverse aortic constriction (TAC) [181]. Upon metformin treatment, the transcription factor SKN-1/NRF2 is activated, resulting in increased expression of antioxidant genes and thus conferring protection against oxidative damage [182]. In dogs, metformin attenuates oxidative stress-induced cardiomyocyte apoptosis and prevents the progression of heart failure along with activation of AMPK [183]. In addition, metformin can slow down the progression of age-related diseases. In the United Kingdom Prospective Diabetes study, patients treated with metformin achieved significantly lower mortality over 10 years of follow-up from myocardial infarction, stroke, or all-causes when compared to patients with sulfonylurea, insulin, or dietary control [184,185].

3.4.3. Berberine

Berberine enhances autophagy through the inhibition of mTOR/AMPK signaling pathway [186], thus limiting the increase in heart size, decreasing collagen deposition, suppressing cardiac apoptosis and fibrosis, and attenuating cardiac dysfunction in rats with TAC-induced cardiac hypertrophy [187] and rats after acute myocardial infarction [188]. Berberine markedly prevents H_2O_2-induced senescence, alleviating the impairment of autophagic flux and restoring NAD^+ levels in senescent cells [189]. In aged mice, berberine alleviates postoperative cognitive dysfunction via the suppression of neuroinflammation [190]. In aged rats, berberine increases the protein expression of pAMPK, SIRT1 and PGC-1α as well as ATP production, ameliorating aging-related decline in skeletal muscular functions [191]. In rats with TAC, berberine ameliorates cardiac dysfunction and prevents the development of left ventricular hypertrophy induced by pressure overload [192]. Lastly, in a study of patients with chronic congestive heart failure (CHF), berberine effectively improves cardiac function and decreases mortality during long-term follow-up [193].

3.4.4. Rapamycin

mTOR is a serine/threonine kinase that functions as a sensor for intracellular energy. Rapamycin is a well-known FDA-approved mTOR inhibitor, initially used clinically as an immunosuppressive drug against allograft rejection in patients. As a potent inducer of autophagy, it extends lifespan in various organisms including yeast, flies, worms, and mice [163,194,195]. The National Institute on Aging (NIA) Intervention Testing Program shows that long-term rapamycin treatment started at 9 or 18 months of age extends lifespan in mice [196,197]. Short-term rapamycin treatment (10 weeks) substantially improves diastolic function and attenuates left ventricular hypertrophy in aged mice [198]. The alleviation of cardiac aging phenotypes by rapamycin treatment is likely linked to proteomic and metabolic remodeling not only by increasing mitochondrial protein content but also reversing the age-related metabolic shift from fatty acid oxidation to glycolysis [199]. Similar effects are observed in younger mice after three-month rapamycin treatment starting at 12 weeks of age [200], indicating the age-irrelevant drug effects of rapamycin on heart weight and dimensional measurements. Notably, long-term administration of rapamycin in some patients has been reported to cause a variety of side effects including impaired wound healing, anemia, proteinuria, pneumonitis, hypercholesterolemia and so forth [163], sending a cautionary note to the attempt to use rapamycin in anti-aging treatment.

4. Concluding marks

Because the incidence of heart diseases significantly increases with age, it is important to clarify the mechanisms of cardiac aging. Multiple lines of evidence in animal models and human have proven that the mitochondria play an important role in cardiac aging. A comprehensive understanding of mitochondrial regulation in cardiac aging will be beneficial for the search of novel mitochondrial-targeted therapeutic strategies to attenuate cardiac aging and to alleviate age-related cardiac diseases.

Competing financial interests

The authors declare no competing financial interests.

Transparency document

The Transparency document associated with this article can be found, in online version.

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References

[1] T.E. Kauppila, J.H. Kauppila, N.G. Larsson, Mammalian mitochondria and aging: an update, Cell Metab. 25 (2017) 57–71.
[2] J. Strait, E. Lakatta, Aging-associated cardiovascular changes and their relationship to heart failure, Heart Fail. Clin. 8 (2012) 143–164.
[3] A. Shirakabe, Y. Ikeda, S. Sciarretta, D. Zablocki, J. Sadoshima, Aging and autophagy in the heart, Circ. Res. 118 (2016) 1563–1576.
[4] M.B. Jensen, H. Jasper, Mitochondrial proteostasis in the control of aging and longevity, Cell Metab. 20 (2014) 214–225.
[5] Y. Wang, S. Hekimi, Mitochondrial dysfunction and longevity in animals: untangling the knot, Science 350 (2015) 1204–1207.
[6] J. Ren, J.R. Sowers, Y. Zhang, Metabolic stress, autophagy, and cardiovascular aging: from pathophysiology to therapeutics, Trends Endocrinol. Metab. 29 (2018) 699–711.
[7] H. Wu, Q. Chen, Hypoxia activation of mitophagy and its role in disease pathogenesis, Antioxid. Redox Signal. 22 (2015) 1032–1046.
[8] R.K. Dongworth, A.R. Hall, N. Burke, D.J. Hausenloy, Targeting mitochondria for cardioprotection: examining the benefit for patients, Futur. Cardiol. 10 (2014) 255–272.
[9] A. Tocchi, E.K. Quarles, N. Basisty, L. Gitari, P.S. Rabinovitch, Mitochondrial dysfunction in cardiac aging, Biochim. Biophys. Acta 1847 (2015) 1424–1433.
[10] K.C. Das, H. Muniyappa, Age-dependent mitochondrial energy dynamics in the mice heart: role of superoxide dismutase-2, Exp. Gerontol. 48 (2013) 947–959.
[11] G.W. Dorn 2nd, Mitochondrial dynamics in heart disease, Biochim. Biophys. Acta 1833 (2013) 233–241.
[12] A. Terman, H. Dalen, J.W. Eaton, J. Neuzil, U.T. Brunk, Mitochondrial recycling and aging of cardiac myocytes: the role of autophagocytosis, Exp. Gerontol. 38 (2003) 863–876.
[13] A. Terman, T. Kurz, M. Navratil, E.A. Arriaga, U.T. Brunk, Mitochondrial turnover and aging of long-lived postmitotic cells: the mitochondrial-lysosomal axis theory of aging, Antioxid. Redox Signal. 12 (2010) 503–535.
[14] R. Ferrari, A. Cargnoni, C. Ceconi, Anti-ischaemic effect of ivabradine, Pharmacol. Res. 53 (2006) 435–439.
[15] F.T. Kurz, M.A. Aon, B. O'Rourke, A.A. Armoundas, Functional implications of cardiac mitochondria clustering, Adv. Exp. Med. Biol. 982 (2017) 1–24.
[16] K.R. Chaudhary, H. El-Sikhry, J.M. Seubert, Mitochondria and the aging heart, J. Geriatr. Cardiol. 8 (2011) 159–167.
[17] D. Harman, The free radical theory of aging, Antioxid. Redox Signal. 5 (2003) 557–561.
[18] C. Franceschi, M. Bonafe, S. Valensin, F. Olivieri, M. De Luca, E. Ottaviani, G. De Benedictis, Inflamm-aging. An evolutionary perspective on immunosenescence, Ann. N. Y. Acad. Sci. 908 (2000) 244–254.
[19] H.Y. Chung, H.J. Kim, J.W. Kim, B.P. Yu, The inflammation hypothesis of aging-molecular modulation by calorie restriction, Ann. N. Y. Acad. Sci. 928 (2001) 327–335.
[20] D.F. Dai, Y.A. Chiao, D.J. Marcinek, H.H. Szeto, P.S. Rabinovitch, Mitochondrial oxidative stress in aging and healthspan, Longev. Healthspan 3 (2014) 6.
[21] A.W. Linnane, T. Ozawa, S. Marzuki, M. Tanaka, Mitochondrial-DNA mutations as an important contributor to ageing and degenerative diseases, Lancet 1 (1989) 642–645.
[22] R.A. Gottlieb, A.B. Gustafsson, Mitochondrial turnover in the heart, Biochim. Biophys. Acta, Mol. Cell Res. 1813 (2011) 1295–1301.
[23] A.B. Harbauer, R.P. Zahedi, A. Sickmann, N. Pfanner, C. Meisinger, The protein import machinery of mitochondria-a regulatory hub in metabolism, stress, and disease, Cell Metab. 19 (2014) 357–372.
[24] P.H. Willems, R. Rossignol, C.E. Dieteren, M.P. Murphy, W.J. Koopman, Redox homeostasis and mitochondrial dynamics, Cell Metab. 22 (2015) 207–218.
[25] J. Moslehi, R.A. DePinho, E. Sahin, Telomeres and mitochondria in the aging heart, Circ. Res. 110 (2012) 1226–1237.
[26] J.W. Palmer, B. Tandler, C.L. Hoppel, Biochemical properties of subsarcolemmal and inter-fibrillar mitochondria isolated from rat cardiac-muscle, J. Biol. Chem. 252 (1977) 8731–8739.
[27] A. Riva, B. Tandler, F. Loffredo, E. Vazquez, C.L. Hoppel, Structural differences in two biochemically defined populations of cardiac mitochondria, Am. J. Physiol. Heart Circ. Physiol. 289 (2005) H868–H872.
[28] M. El'darov Ch, V.B. Vays, I.M. Vangeli, N.G. Kolosova, L.E. Bakeeva, Morphometric examination of mitochondrial ultrastructure in aging cardiomyocytes, Biochemistry (Mosc) 80 (2015) 604–609.
[29] H. Frenzel, J. Feimann, Age-dependent structural changes in the myocardium of rats. A quantitative light- and electron-microscopic study on the right and left chamber wall, Mech. Ageing Dev. 27 (1984) 29–41.
[30] S.W. Fannin, E.J. Lesnefsky, T.J. Slabe, M.O. Hassan, C.L. Hoppel, Aging selectively decreases oxidative capacity in rat heart interfibrillar mitochondria, Arch. Biochem. Biophys. 372 (1999) 399–407.
[31] A. Riva, B. Tandler, E.J. Lesnefsky, G. Conti, F. Loffredo, E. Vazquez, C.L. Hoppel, Structure of cristae in cardiac mitochondria of aged rat, Mech. Ageing Dev. 127 (2006) 917–921.
[32] M.P. Murphy, How mitochondria produce reactive oxygen species, Biochem. J. 417 (2009) 1–13.
[33] S. Matsuzaki, P.A. Szweda, L.I. Szweda, K.M. Humphries, Regulated production of free radicals by the mitochondrial electron transport chain: cardiac ischemic preconditioning, Adv. Drug Deliv. Rev. 61 (2009) 1324–1331.
[34] R.S. Sohal, W.C. Orr, The redox stress hypothesis of aging, Free Radic. Biol. Med. 52 (2012) 539–555.
[35] S.E. Schriner, N.J. Linford, G.M. Martin, P. Treuting, C.E. Ogburn, M.J. Emond, P.E. Coskun, W. Ladiges, N. Wolf, H. Van Remmen, D.C. Wallace, P.S. Rabinovitch, Extension of murine life span by overexpression of catalase targeted to mitochondria, Science 308 (2005) 1909–1911.
[36] G.C. Kujoth, A. Hiona, T.D. Pugh, S. Someya, K. Panzer, S.E. Wohlgemuth, T. Hofer, A.Y. Seo, R. Sullivan, W.A. Jobling, J.D. Morrow, H. Van Remmen, J.M. Sedivy, T. Yamasoba, M. Tanokura, R. Weindruch, C. Leeuwenburgh, T.A. Prolla, Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging, Science 309 (2005) 481–484.
[37] D.F. Dai, L.F. Santana, M. Vermulst, D.M. Tomazela, M.J. Emond, M.J. MacCoss, K. Gollahon, G.M. Martin, L.A. Loeb, W. Ladiges, P.S. Rabinovitch, Overexpression of catalase targeted to mitochondria attenuates murine cardiac aging, Circulation 119 (2009) 2789–2797.
[38] T. Ago, J. Kuroda, J. Pain, C. Fu, H. Li, J. Sadoshima, Upregulation of Nox4 by hypertrophic stimuli promotes apoptosis and mitochondrial dysfunction in cardiac myocytes, Circ. Res. 106 (2010) (1253-1183).
[39] Y.C. Jang, V.I. Perez, W. Song, M.S. Lustgarten, A.B. Salmon, J. Mele, W. Qi, Y. Liu, H. Liang, A. Chaudhuri, Y. Ikeno, C.J. Epstein, H. Van Remmen, A. Richardson, Overexpression of Mn superoxide dismutase does not increase life span in mice, J.

Gerontol. A Biol. Sci. Med. Sci. 64 (2009) 1114–1125.
[40] J. Yun, T. Finkel, Mitohormesis, Cell Metab. 19 (2014) 757–766.
[41] M. Ristow, Mitohormesis explains ROS-induced health benefits, Nat. Med. 20 (2014) 709–711.
[42] S. Schmeisser, K. Schmeisser, S. Weimer, M. Groth, S. Priebe, E. Fazius, D. Kuhlow, D. Pick, J.W. Einax, R. Guthke, M. Platzer, K. Zarse, M. Ristow, Mitochondrial hormesis links low-dose arsenite exposure to lifespan extension, Aging Cell 12 (2013) 508–517.
[43] M. Xie, R. Roy, Increased levels of hydrogen peroxide induce a HIF-1-dependent modification of lipid metabolism in AMPK compromised *C. elegans* Dauer larvae, Cell Metab. 16 (2012) 322–335.
[44] M. Song, Y. Chen, G. Gong, E. Murphy, P.S. Rabinovitch, G.W. Dorn 2nd, Super-suppression of mitochondrial reactive oxygen species signaling impairs compensatory autophagy in primary mitophagic cardiomyopathy, Circ. Res. 115 (2014) 348–353.
[45] X. Xu, S. Duan, F. Yi, A. Ocampo, G.H. Liu, J.C. Izpisua Belmonte, Mitochondrial regulation in pluripotent stem cells, Cell Metab. 18 (2013) 325–332.
[46] M. Corraldebrinski, J.M. Shoffner, M.T. Lott, D.C. Wallace, Association of mitochondrial-DNA damage with aging and coronary atherosclerotic heart-disease, Mutat. Res. 275 (1992) 169–180.
[47] J. Wanagat, Z. Cao, P. Pathare, J. Aiken, Mitochondrial DNA deletion mutations colocalize with segmental electron transport system abnormalities, muscle fiber atrophy, fiber splitting, and oxidative damage in sarcopenia, FASEB J. 15 (2001) 322–332.
[48] M. Khaidakov, R.H. Heflich, M.G. Manjanatha, M.B. Myers, A. Aidoo, Accumulation of point mutations in mitochondrial DNA of aging mice, Mutat. Res. 526 (2003) 1–7.
[49] A. Lauri, G. Pompilio, M.C. Capogrossi, The mitochondrial genome in aging and senescence, Ageing Res. Rev. 18 (2014) 1–15.
[50] A. Trifunovic, A. Wredenberg, M. Falkenberg, J.N. Spelbrink, A.T. Rovio, C.E. Bruder, Y.M. Bohlooly, S. Gidlof, A. Oldfors, R. Wibom, J. Tornell, H.T. Jacobs, N.G. Larsson, Premature ageing in mice expressing defective mitochondrial DNA polymerase, Nature 429 (2004) 417–423.
[51] M. Vermulst, J. Wanagat, G.C. Kujoth, J.H. Bielas, P.S. Rabinovitch, T.A. Prolla, L.A. Loeb, DNA deletions and clonal mutations drive premature aging in mitochondrial mutator mice, Nat. Genet. 40 (2008) 392–394.
[52] D.F. Dai, T. Chen, J. Wanagat, M. Laflamme, D.J. Marcinek, M.J. Emond, C. Ngo, T.A. Prolla, P.S. Rabinovitch, Age-dependent cardiomyopathy in mitochondrial mutator mice is attenuated by overexpression of catalase targeted to mitochondria, Aging Cell 9 (2010) 536–544.
[53] R.D. Martinus, G.P. Garth, T.L. Webster, P. Cartwright, D.J. Naylor, P.B. Hoj, N.J. Hoogenraad, Selective induction of mitochondrial chaperones in response to loss of the mitochondrial genome, Eur. J. Biochem. 240 (1996) 98–103.
[54] C.M. Haynes, D. Ron, The mitochondrial UPR-protecting organelle protein homeostasis, J. Cell Sci. 123 (2010) 3849–3855.
[55] C.M. Haynes, C.J. Fiorese, Y.F. Lin, Evaluating and responding to mitochondrial dysfunction: the mitochondrial unfolded-protein response and beyond, Trends Cell Biol. 23 (2013) 311–318.
[56] Q. Zhao, J. Wang, I.V. Levichkin, S. Stasinopoulos, M.T. Ryan, N.J. Hoogenraad, A mitochondrial specific stress response in mammalian cells, EMBO J. 21 (2002) 4411–4419.
[57] R.H. Houtkooper, L. Mouchiroud, D. Ryu, N. Moullan, E. Katsyuba, G. Knott, R.W. Williams, J. Auwerx, Mitonuclear protein imbalance as a conserved longevity mechanism, Nature 497 (2013) 451–457.
[58] V. Jovaisaite, J. Auwerx, The mitochondrial unfolded protein response-synchronizing genomes, Curr. Opin. Cell Biol. 33 (2015) 74–81.
[59] E.D. Runkel, S. Liu, R. Baumeister, E. Schulze, Surveillance-activated defenses block the ROS-induced mitochondrial unfolded protein response, PLoS Genet. 9 (2013) e1003346.
[60] D.A. Pulliam, S.S. Deepa, Y. Liu, S. Hill, A.L. Lin, A. Bhattacharya, Y. Shi, L. Sloane, C. Viscomi, M. Zeviani, H. Van Remmen, Complex IV-deficient Surf1(−/−) mice initiate mitochondrial stress responses, Biochem. J. 462 (2014) 359–371.
[61] S.A. Dogan, C. Pujol, P. Maiti, A. Kukat, S. Wang, S. Hermans, K. Senft, R. Wibom, E.I. Rugarli, A. Trifunovic, Tissue-specific loss of DARS2 activates stress responses independently of respiratory chain deficiency in the heart, Cell Metab. 19 (2014) 458–469.
[62] A. Dillin, A.L. Hsu, N.A. Arantes-Oliveira, J. Lehrer-Graiwer, H. Hsin, A.G. Fraser, R.S. Kamath, J. Ahringer, C. Kenyon, Rates of behavior and aging specified by mitochondrial function during development, Science 298 (2002) 2398–2401.
[63] E. Owusu-Ansah, W. Song, N. Perrimon, Muscle mitohormesis promotes longevity via systemic repression of insulin signaling, Cell 155 (2013) 699–712.
[64] B.M. Baker, A.M. Nargund, T. Sun, C.M. Haynes, Protective coupling of mitochondrial function and protein synthesis via the eIF2α kinase GCN-2, PLoS Genet. 8 (2012) e1002760.
[65] J. Durieux, S. Wolff, A. Dillin, The cell-non-autonomous nature of electron transport chain-mediated longevity, Cell 144 (2011) 79–91.
[66] M. Song, A. Franco, J.A. Fleischer, L. Zhang, G.W. Dorn 2nd, Abrogating mitochondrial dynamics in mouse hearts accelerates mitochondrial senescence, Cell Metab. 26 (2017) 872–883.e5.
[67] K.D. Salway, E.J. Gallagher, M.M. Page, J.A. Stuart, Higher levels of heat shock proteins in longer-lived mammals and birds, Mech. Ageing Dev. 132 (2011) 287–297.
[68] E. Verdin, NAD(+) in aging, metabolism, and neurodegeneration, Science 350 (2015) 1208–1213.
[69] A. Garten, S. Schuster, M. Penke, T. Gorski, T. de Giorgis, W. Kiess, Physiological and pathophysiological roles of NAMPT and NAD metabolism, Nat. Rev. Endocrinol. 11 (2015) 535–546.
[70] T. Yamamoto, J. Byun, P. Zhai, Y. Ikeda, S. Oka, J. Sadoshima, Nicotinamide mononucleotide, an intermediate of NAD+ synthesis, protects the heart from ischemia and reperfusion, PLoS One 9 (2014) e98972.
[71] C.P. Hsu, S. Oka, D. Shao, N. Hariharan, J. Sadoshima, Nicotinamide phosphoribosyltransferase regulates cell survival through NAD(+) synthesis in cardiac myocytes, Circ. Res. 105 (2009) 481–491.
[72] H. Yang, T. Yang, J.A. Baur, E. Perez, T. Matsui, J.J. Carmona, D.W. Lamming, N.C. Souza-Pinto, V.A. Bohr, A. Rosenzweig, R. de Cabo, A.A. Sauve, D.A. Sinclair, Nutrient-sensitive mitochondrial NAD+ levels dictate cell survival, Cell 130 (2007) 1095–1107.
[73] L. Mouchiroud, R.H. Houtkooper, N. Moullan, E. Katsyuba, D. Ryu, C. Canto, A. Mottis, Y.S. Jo, M. Viswanathan, K. Schoonjans, L. Guarente, J. Auwerx, The NAD(+)/sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling, Cell 154 (2013) 430–441.
[74] C. Cencioni, F. Spallotta, A. Mai, F. Martelli, A. Farsetti, A.M. Zeiher, C. Gaetano, Sirtuin function in aging heart and vessels, J. Mol. Cell. Cardiol. 83 (2015) 55–61.
[75] S. Park, R. Mori, I. Shimokawa, Do sirtuins promote mammalian longevity? A critical review on its relevance to the longevity effect induced by calorie restriction, Mol. Cells 35 (2013) 474–480.
[76] S. Matsushima, J. Sadoshima, The role of sirtuins in cardiac disease, Am. J. Physiol. Heart Circ. Physiol. 309 (2015) H1375–H1389.
[77] E. Michishita, J.Y. Park, J.M. Burneskis, J.C. Barrett, I. Horikawa, Evolutionarily conserved and nonconserved cellular localizations and functions of human SIRT proteins, Mol. Biol. Cell 16 (2005) 4623–4635.
[78] S. Imai, C.M. Armstrong, M. Kaeberlein, L. Guarente, Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase, Nature 403 (2000) 795–800.
[79] R.A. Mathias, T.M. Greco, A. Oberstein, H.G. Budayeva, R. Chakrabarti, E.A. Rowland, Y.B. Kang, T. Shenk, I.M. Cristea, Sirtuin 4 is a lipoamidase regulating pyruvate dehydrogenase complex activity, Cell 159 (2014) 1615–1625.
[80] A. Schuetz, J. Min, T. Antoshenko, C.L. Wang, A. Allali-Hassani, A. Dong, P. Loppnau, M. Vedadi, A. Bochkarev, R. Sternglanz, A.N. Plotnikov, Structural basis of inhibition of the human NAD(+)-dependent deacetylase SIRT5 by suramin, Structure 15 (2007) 377–389.
[81] N. Ahuja, B. Schwer, S. Carobbio, D. Waltregny, B.J. North, V. Castronovo, P. Maechler, E. Verdin, Regulation of insulin secretion by SIRT4, a mitochondrial ADP-ribosyltransferase, J. Biol. Chem. 282 (2007) 33583–33592.
[82] C. Peng, Z. Lu, Z. Xie, Z. Cheng, Y. Chen, M. Tan, H. Luo, Y. Zhang, W. He, K. Yang, B.M. Zwaans, D. Tishkoff, L. Ho, D. Lombard, T.C. He, J. Dai, E. Verdin, Y. Ye, Y. Zhao, The first identification of lysine malonylation substrates and its regulatory enzyme, Mol. Cell. Proteomics 10 (2011) M111.012658.
[83] T. Finkel, C.X. Deng, R. Mostoslavsky, Recent progress in the biology and physiology of sirtuins, Nature 460 (2009) 587–591.
[84] R.R. Alcendor, S. Gao, P. Zhai, D. Zablocki, E. Holle, X. Yu, B. Tian, T. Wagner, S.F. Vatner, J. Sadoshima, SIRT1 regulates aging and resistance to oxidative stress in the heart, Circ. Res. 100 (2007) 1512–1521.
[85] C.P. Hsu, P. Zhai, T. Yamamoto, Y. Maejima, S. Matsushima, N. Hariharan, D. Shao, H. Takagi, S. Oka, J. Sadoshima, Silent information regulator 1 protects the heart from ischemia/reperfusion, Circulation 122 (2010) 2170–2182.
[86] I. Mattagajasingh, C.S. Kim, A. Naqvi, T. Yamamori, T.A. Hoffman, S.B. Jung, J. DeRicco, K. Kasuno, K. Irani, SIRT1 promotes endothelium-dependent vascular relaxation by activating endothelial nitric oxide synthase, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 14855–14860.
[87] J.B. Pillai, A. Isbatan, S. Imai, M.P. Gupta, Poly(ADP-ribose) polymerase-1-dependent cardiac myocyte cell death during heart failure is mediated by NAD+ depletion and reduced Sir2alpha deacetylase activity, J. Biol. Chem. 280 (2005) 43121–43130.
[88] U. Kolthur-Seetharam, F. Dantzer, M.W. McBurney, G. de Murcia, P. Sassone-Corsi, Control of AIF-mediated cell death by the functional interplay of SIRT1 and PARP-1 in response to DNA damage, Cell Cycle 5 (2006) 873–877.
[89] L. Zhang, J. Zou, E. Chai, Y. Qi, Y. Zhang, Alpha-lipoic acid attenuates cardiac hypertrophy via downregulation of PARP-2 and subsequent activation of SIRT-1, Eur. J. Pharmacol. 744 (2014) 203–210.
[90] W. Li, B. Zhang, J. Tang, Q. Cao, Y. Wu, C. Wu, J. Guo, E.A. Ling, F. Liang, Sirtuin 2, a mammalian homolog of yeast silent information regulator-2 longevity regulator, is an oligodendroglial protein that decelerates cell differentiation through deacetylating alpha-tubulin, J. Neurosci. 27 (2007) 2606–2616.
[91] B.J. North, B.L. Marshall, M.T. Borra, J.M. Denu, E. Verdin, The human Sir2 ortholog, SIRT2, is an NAD(+)-dependent tubulin deacetylase, Mol. Cell 11 (2003) 437–444.
[92] E. Jing, S. Gesta, C.R. Kahn, SIRT2 regulates adipocyte differentiation through FoxO1 acetylation/deacetylation, Cell Metab. 6 (2007) 105–114.
[93] A. Vaquero, M.B. Scher, D.H. Lee, A. Sutton, H.L. Cheng, F.W. Alt, L. Serrano, R. Sternglanz, D. Reinberg, SIRT2 is a histone deacetylase with preference for histone H4 Lys 16 during mitosis, Genes Dev. 20 (2006) 1256–1261.
[94] M. Sarikhani, S. Maity, S. Mishra, A. Jain, A.K. Tamta, V. Ravi, M.S. Kondapalli, P.A. Desingu, D. Khan, S. Kumar, S. Rao, M. Inbaraj, A.S. Pandit, N.R. Sundaresan, SIRT2 deacetylase represses NFAT transcription factor to maintain cardiac homeostasis, J. Biol. Chem. 293 (2018) 5281–5294.
[95] X. Tang, X. Chen, N. Wang, X. Wang, S. Liang, W. Zheng, Y. Lu, X. Zhao, D. Hao, Z. Zhang, M. Zou, D. Liu, H.Z. Chen, SIRT2 acts as a cardioprotective deacetylase in pathological cardiac hypertrophy, Circulation 136 (2017) 2051–2067.
[96] D. Bellizzi, G. Rose, P. Cavalcante, G. Covello, S. Dato, F. De Rango, V. Greco, M. Maggiolini, E. Feraco, V. Mari, C. Franceschi, G. Passarino, G. De Benedictis, A novel VNTR enhancer within the SIRT3 gene, a human homologue of SIR2, is

associated with survival at oldest ages, Genomics 85 (2005) 258–263.
[97] M.D. Hirschey, T. Shimazu, J.Y. Huang, E. Verdin, Acetylation of mitochondrial proteins, Methods Enzymol. 457 (2009) 137–147.
[98] X. Kong, R. Wang, Y. Xue, X. Liu, H. Zhang, Y. Chen, F. Fang, Y. Chang, Sirtuin 3, a new target of PGC-1 alpha, plays an important role in the suppression of ROS and mitochondrial biogenesis, PLoS One 5 (2010) e11707.
[99] T. Shi, F. Wang, E. Stieren, Q. Tong, SIRT3, a mitochondrial sirtuin deacetylase, regulates mitochondrial function and thermogenesis in brown adipocytes, J. Biol. Chem. 280 (2005) 13560–13567.
[100] T. Shimazu, M.D. Hirschey, L. Hua, K.E. Dittenhafer-Reed, B. Schwer, D.B. Lombard, Y. Li, J. Bunkenborg, F.W. Alt, J.M. Denu, M.P. Jacobson, E. Verdin, SIRT3 deacetylates mitochondrial 3-hydroxy-3-methylglutaryl CoA synthase 2 and regulates ketone body production, Cell Metab. 12 (2010) 654–661.
[101] M.J. Rardin, W. He, Y. Nishida, J.C. Newman, C. Carrico, S.R. Danielson, A. Guo, P. Gut, A.K. Sahu, B. Li, R. Uppala, M. Fitch, T. Riiff, L. Zhu, J. Zhou, D. Mulhern, R.D. Stevens, O.R. Ilkayeva, C.B. Newgard, M.P. Jacobson, M. Hellerstein, E.S. Goetzman, B.W. Gibson, E. Verdin, SIRT5 regulates the mitochondrial lysine succinylome and metabolic networks, Cell Metab. 18 (2013) 920–933.
[102] W.C. Hallows, W. Yu, B.C. Smith, M.K. Devries, J.J. Ellinger, S. Someya, M.R. Shortreed, T.A. Prolla, J.L. Markley, L.M. Smith, S. Zhao, K.L. Guan, J.M. Denu, SIRT3 promotes the urea cycle and fatty acid oxidation during dietary restriction, Mol. Cell 41 (2011) 139–149.
[103] B.H. Ahn, H.S. Kim, S. Song, I.H. Lee, J. Liu, A. Vassilopoulos, C.X. Deng, T. Finkel, A role for the mitochondrial deacetylase Sirt3 in regulating energy homeostasis, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 14447–14452.
[104] X. Wang, Y. Shao, C. Ma, W. Chen, L. Sun, W. Liu, D. Zhang, B. Fu, K. Liu, Z. Jia, B. Xie, S. Jiang, R. Li, H. Tian, Decreased SIRT3 in aged human mesenchymal stromal/stem cells increases cellular susceptibility to oxidative stress, J. Cell. Mol. Med. 18 (2014) 2298–2310.
[105] N.R. Sundaresan, S.A. Samant, V.B. Pillai, S.B. Rajamohan, M.P. Gupta, SIRT3 is a stress-responsive deacetylase in cardiomyocytes that protects cells from stress-mediated cell death by deacetylation of Ku70, Mol. Cell. Biol. 28 (2008) 6384–6401.
[106] N.R. Sundaresan, S. Bindu, V.B. Pillai, S. Samant, Y. Pan, J.Y. Huang, M. Gupta, R.S. Nagalingam, D. Wolfgeher, E. Verdin, M.P. Gupta, SIRT3 blocks aging-associated tissue fibrosis in mice by deacetylating and activating glycogen synthase kinase 3β, Mol. Cell. Biol. 36 (2015) 678–692.
[107] N.R. Sundaresan, M. Gupta, G. Kim, S.B. Rajamohan, A. Isbatan, M.P. Gupta, SIRT3 blocks the cardiac hypertrophic response by augmenting Foxo3a-dependent antioxidant defense mechanisms in mice, J. Clin. Invest. 119 (2009) 2758–2771.
[108] L.W. Finley, A. Carracedo, J. Lee, A. Souza, A. Egia, J. Zhang, J. Teruya-Feldstein, P.I. Moreira, S.M. Cardoso, C.B. Clish, P.P. Pandolfi, M.C. Haigis, SIRT3 opposes reprogramming of cancer cell metabolism through HIF1 alpha destabilization, Cancer Cell 19 (2011) 416–428.
[109] A.V. Hafner, J. Dai, A.P. Gomes, C.Y. Xiao, C.M. Palmeira, A. Rosenzweig, D.A. Sinclair, Regulation of the mPTP by SIRT3-mediated deacetylation of CypD at lysine 166 suppresses age-related cardiac hypertrophy, Aging (Albany NY) 2 (2010) 914–923.
[110] M.C. Haigis, R. Mostoslavsky, K.M. Haigis, K. Fahie, D.C. Christodoulou, A.J. Murphy, D.M. Valenzuela, G.D. Yancopoulos, M. Karow, G. Blander, C. Wolberger, T.A. Prolla, R. Weindruch, F.W. Alt, L. Guarente, SIRT4 inhibits glutamate dehydrogenase and opposes the effects of calorie restriction in pancreatic beta cells, Cell 126 (2006) 941–954.
[111] G. Laurent, N.J. German, A.K. Saha, V.C. de Boer, M. Davies, T.R. Koves, N. Dephoure, F. Fischer, G. Boanca, B. Vaitheesvaran, S.B. Lovitch, A.H. Sharpe, I. Kurland, C. Steegborn, S.P. Gygi, D.M. Muoio, N.B. Ruderman, M.C. Haigis, SIRT4 coordinates the balance between lipid synthesis and catabolism by repressing malonyl CoA decarboxylase, Mol. Cell 50 (2013) 686–698.
[112] N. Nasrin, X. Wu, E. Fortier, Y. Feng, O.C. Bare, S. Chen, X. Ren, Z. Wu, R.S. Streeper, L. Bordone, SIRT4 regulates fatty acid oxidation and mitochondrial gene expression in liver and muscle cells, J. Biol. Chem. 285 (2010) 31995–32002.
[113] B. Liu, W. Che, J. Xue, C. Zheng, K. Tang, J. Zhang, J. Wen, Y. Xu, SIRT4 prevents hypoxia-induced apoptosis in H9c2 cardiomyoblast cells, Cell. Physiol. Biochem. 32 (2013) 655–662.
[114] G. Zeng, H. Liu, H. Wang, Amelioration of myocardial ischemia-reperfusion injury by SIRT4 involves mitochondrial protection and reduced apoptosis, Biochem. Biophys. Res. Commun. 502 (2018) 15–21.
[115] M. Tan, C. Peng, K.A. Anderson, P. Chhoy, Z. Xie, L. Dai, J. Park, Y. Chen, H. Huang, Y. Zhang, J. Ro, G.R. Wagner, M.F. Green, A.S. Madsen, J. Schmiesing, B.S. Peterson, G. Xu, O.R. Ilkayeva, M.J. Muehlbauer, T. Braulke, C. Muhlhausen, D.S. Backos, C.A. Olsen, P.J. McGuire, S. Pletcher, D.B. Lombard, M.D. Hirschey, Y. Zhao, Lysine glutarylation is a protein posttranslational modification regulated by SIRT5, Cell Metab. 19 (2014) 605–617.
[116] B. Liu, W. Che, C. Zheng, W. Liu, J. Wen, H. Fu, K. Tang, J. Zhang, Y. Xu, SIRT5: a safeguard against oxidative stress-induced apoptosis in cardiomyocytes, Cell. Physiol. Biochem. 32 (2013) 1050–1059.
[117] R. Mostoslavsky, K.F. Chua, D.B. Lombard, W.W. Pang, M.R. Fischer, L. Gellon, P. Liu, G. Mostoslavsky, S. Franco, M.M. Murphy, K.D. Mills, P. Patel, J.T. Hsu, A.L. Hong, E. Ford, H.L. Cheng, C. Kennedy, N. Nunez, R. Bronson, D. Frendewey, W. Auerbach, D. Valenzuela, M. Karow, M.O. Hottiger, S. Hursting, J.C. Barrett, L. Guarente, R. Mulligan, B. Demple, G.D. Yancopoulos, F.W. Alt, Genomic instability and aging-like phenotype in the absence of mammalian SIRT6, Cell 124 (2006) 315–329.
[118] C. Xiao, H.S. Kim, T. Lahusen, R. Wang, X. Xu, O. Gavrilova, W. Jou, D. Gius, C.X. Deng, SIRT6 deficiency results in severe hypoglycemia by enhancing both basal and insulin-stimulated glucose uptake in mice, J. Biol. Chem. 285 (2010) 36776–36784.
[119] E. Michishita, R.A. McCord, E. Berber, M. Kioi, H. Padilla-Nash, M. Damian, P. Cheung, R. Kusumoto, T.L.A. Kawahara, J.C. Barrett, H.Y. Chang, V.A. Bohr, T. Ried, O. Gozani, K.F. Chua, SIRT6 is a histone H3 lysine 9 deacetylase that modulates telomeric chromatin, Nature 452 (2008) 492–496.
[120] R.A. McCord, E. Michishita, T. Hong, E. Berber, L.D. Boxer, R. Kusumoto, S. Guan, X. Shi, O. Gozani, A.L. Burlingame, V.A. Bohr, K.F. Chua, SIRT6 stabilizes DNA-dependent protein kinase at chromatin for DNA double-strand break repair, Aging (Albany NY) 1 (2009) 109–121.
[121] A. Kaidi, B.T. Weinert, C. Choudhary, S.P. Jackson, Human SIRT6 promotes DNA end resection through CtIP deacetylation, Science 329 (2010) 1348–1353.
[122] G. Liszt, E. Ford, M. Kurtev, L. Guarente, Mouse Sir2 homolog SIRT6 is a nuclear ADP-ribosyltransferase, J. Biol. Chem. 280 (2005) 21313–21320.
[123] E. Michishita, R.A. McCord, L.D. Boxer, M.F. Barber, T. Hong, O. Gozani, K.F. Chua, Cell cycle-dependent deacetylation of telomeric histone H3 lysine K56 by human SIRT6, Cell Cycle 8 (2009) 2664–2666.
[124] L. Zhong, A. D'Urso, D. Toiber, C. Sebastian, R.E. Henry, D.D. Vadysirisack, A. Guimaraes, B. Marinelli, J.D. Wikstrom, T. Nir, C.B. Clish, B. Vaitheesvaran, O. Iliopoulos, I. Kurland, Y. Dor, R. Weissleder, O.S. Shirihai, L.W. Ellisen, J.M. Espinosa, R. Mostoslavsky, The histone deacetylase SIRT6 regulates glucose homeostasis via Hif1 alpha, Cell 140 (2010) 280–293.
[125] E. Ford, R. Voit, G. Liszt, C. Magin, I. Grummt, L. Guarente, Mammalian Sir2 homolog SIRT7 is an activator of RNA polymerase I transcription, Genes Dev. 20 (2006) 1075–1080.
[126] O. Vakhrusheva, C. Smolka, P. Gajawada, S. Kostin, T. Boettger, T. Kubin, T. Braun, E. Bober, SIRT7 increases stress resistance of cardiomyocytes and prevents apoptosis and inflammatory cardiomyopathy in mice, Circ. Res. 102 (2008) 703–710.
[127] B. Levine, N. Mizushima, H.W. Virgin, Autophagy in immunity and inflammation, Nature 469 (2011) 323–335.
[128] N. Mizushima, B. Levine, A.M. Cuervo, D.J. Klionsky, Autophagy fights disease through cellular self-digestion, Nature 451 (2008) 1069–1075.
[129] X. Xu, J. Pang, Y. Chen, R. Bucala, Y. Zhang, J. Ren, Macrophage migration inhibitory factor (MIF) deficiency exacerbates aging-induced cardiac remodeling and dysfunction despite improved inflammation: role of autophagy regulation, Sci. Rep. 6 (2016) 22488.
[130] Y. Zhang, C. Wang, J. Zhou, A. Sun, L.K. Hueckstaedt, J. Ge, J. Ren, Complex inhibition of autophagy by mitochondrial aldehyde dehydrogenase shortens lifespan and exacerbates cardiac aging, Biochim. Biophys. Acta Mol. basis Dis. 1863 (2017) 1919–1932.
[131] J. Ren, L. Yang, L. Zhu, X. Xu, A.F. Ceylan, W. Guo, J. Yang, Y. Zhang, Akt2 ablation prolongs life span and improves myocardial contractile function with adaptive cardiac remodeling: role of Sirt1-mediated autophagy regulation, Aging Cell 16 (2017) 976–987.
[132] R.J. Youle, A.M. van der Bliek, Mitochondrial fission, fusion, and stress, Science 337 (2012) 1062–1065.
[133] S.M. Jin, M. Lazarou, C. Wang, L.A. Kane, D.P. Narendra, R.J. Youle, Mitochondrial membrane potential regulates PINK1 import and proteolytic destabilization by PARL, J. Cell Biol. 191 (2010) 933–942.
[134] M. Lazarou, S.M. Jin, L.A. Kane, R.J. Youle, Role of PINK1 binding to the TOM complex and alternate intracellular membranes in recruitment and activation of the E3 ligase PARKIN, Dev. Cell 22 (2012) 320–333.
[135] G. Gong, M. Song, G. Csordas, D.P. Kelly, S.J. Matkovich, G.W. Dorn 2nd, PARKIN-mediated mitophagy directs perinatal cardiac metabolic maturation in mice, Science 350 (2015) aad2459.
[136] Y. Chen, G.W. Dorn 2nd, PINK1-phosphorylated mitofusin 2 is a PARKIN receptor for culling damaged mitochondria, Science 340 (2013) 471–475.
[137] E.J. Lesnefsky, Q. Chen, C.L. Hoppel, Mitochondrial metabolism in aging heart, Circ. Res. 118 (2016) 1593–1611.
[138] K. Palikaras, E. Lionaki, N. Tavernarakis, Coordination of mitophagy and mitochondrial biogenesis during ageing in *C. elegans*, Nature 521 (2015) 525–528.
[139] D.A. Kubli, M.N. Quinsay, A.B. Gustafsson, PARKIN deficiency results in accumulation of abnormal mitochondria in aging myocytes, Commun. Integr. Biol. 6 (2013) e24511.
[140] H. Liu, Z. He, H.U. Simon, Protective role of autophagy and autophagy-related protein 5 in early tumorigenesis, J. Mol. Med. (Berl.) 93 (2015) 159–164.
[141] M. Taneike, O. Yamaguchi, A. Nakai, S. Hikoso, T. Takeda, I. Mizote, T. Oka, T. Tamai, J. Oyabu, T. Murakawa, K. Nishida, T. Shimizu, M. Hori, I. Komuro, T.S. Takuji Shirasawa, N. Mizushima, K. Otsu, Inhibition of autophagy in the heart induces age-related cardiomyopathy, Autophagy 6 (2010) 600–606.
[142] J.O. Pyo, S.M. Yoo, H.H. Ahn, J. Nah, S.H. Hong, T.I. Kam, S. Jung, Y.K. Jung, Overexpression of Atg5 in mice activates autophagy and extends lifespan, Nat. Commun. 4 (2013) 2300.
[143] V.J. Cadete, S. Deschenes, A. Cuillerier, F. Brisebois, A. Sugiura, A. Vincent, D. Turnbull, M. Picard, H.M. McBride, Y. Burelle, Formation of mitochondrial-derived vesicles is an active and physiologically relevant mitochondrial quality control process in the cardiac system, J. Physiol. 594 (2016) 5343–5362.
[144] A. Sugiura, G.L. McLelland, E.A. Fon, H.M. McBride, A new pathway for mitochondrial quality control: mitochondrial-derived vesicles, EMBO J. 33 (2014) 2142–2156.
[145] V. Soubannier, G.L. McLelland, R. Zunino, E. Braschi, P. Rippstein, E.A. Fon, H.M. McBride, A vesicular transport pathway shuttles cargo from mitochondria to lysosomes, Curr. Biol. 22 (2012) 135–141.
[146] G.L. McLelland, V. Soubannier, C.X. Chen, H. McBride, E.A. Fon, PARKIN and PINK1 function in a vesicular trafficking pathway regulating mitochondrial quality control, EMBO J. 33 (2014) 282–295.

[147] E.V. Menshikova, V.B. Ritov, L. Fairfull, R.E. Ferrell, D.E. Kelley, B.H. Goodpaster, Effects of exercise on mitochondrial content and function in aging human skeletal muscle, J. Gerontol. A Biol. Sci. Med. Sci. 61 (2006) 534–540.
[148] J.C. Eisele, I.M. Schaefer, J.R. Nyengaard, H. Post, D. Liebetanz, A. Brul, C. Muhlfeld, Effect of voluntary exercise on number and volume of cardiomyocytes and their mitochondria in the mouse left ventricle, Basic Res. Cardiol. 103 (2008) 12–21.
[149] A. Safdar, J. Bourgeois, D.I. Ogborn, J.P. Little, B.P. Hettinga, M. Akhtar, J.E. Thompson, S. Melov, N.J. Mocellin, G.C. Kujoth, T.A. Prolla, M.A. Tarnopolsky, Endurance exercise rescues progeroid aging and induces systemic mitochondrial rejuvenation in mtDNA mutator mice, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 4135–4140.
[150] A. Safdar, J.P. Little, A.J. Stokl, B.P. Hettinga, M. Akhtar, M.A. Tarnopolsky, Exercise increases mitochondrial PGC-1 alpha content and promotes nuclear-mitochondrial cross-talk to coordinate mitochondrial biogenesis, J. Biol. Chem. 286 (2011) 10605–10617.
[151] J.R. Speakman, S.E. Mitchell, Caloric restriction, Mol. Asp. Med. 32 (2011) 159–221.
[152] B.J. Merry, Oxidative stress and mitochondrial function with aging-the effects of calorie restriction, Aging Cell 3 (2004) 7–12.
[153] E.J. Masoro, Overview of caloric restriction and ageing, Mech. Ageing Dev. 126 (2005) 913–922.
[154] K. Shinmura, K. Tamaki, M. Sano, M. Murata, H. Yamakawa, H. Ishida, K. Fukuda, Impact of long-term caloric restriction on cardiac senescence: caloric restriction ameliorates cardiac diastolic dysfunction associated with aging, J. Mol. Cell. Cardiol. 50 (2011) 117–127.
[155] E.P. Weiss, L. Fontana, Caloric restriction: powerful protection for the aging heart and vasculature, Am. J. Physiol. Heart Circ. Physiol. 301 (2011) H1205–H1219.
[156] R. Gredilla, A. Sanz, M. Lopez-Torres, G. Barja, Caloric restriction decreases mitochondrial free radical generation at complex I and lowers oxidative damage to mitochondrial DNA in the rat heart, FASEB J. 15 (2001) 1589–1591.
[157] A.J. Lambert, B. Wang, J. Yardley, J. Edwards, B.J. Merry, The effect of aging and caloric restriction on mitochondrial protein density and oxygen consumption, Exp. Gerontol. 39 (2004) 289–295.
[158] B. Niemann, Y. Chen, H. Issa, R.E. Silber, S. Rohrbach, Caloric restriction delays cardiac ageing in rats: role of mitochondria, Cardiovasc. Res. 88 (2010) 267–276.
[159] A. Sanz, R. Gredilla, R. Pamplona, M. Portero-Otin, E. Vara, J.A. Tresguerres, G. Barja, Effect of insulin and growth hormone on rat heart and liver oxidative stress in control and caloric restricted animals, Biogerontology 6 (2005) 15–26.
[160] K. Shinmura, K. Tamaki, M. Sano, N. Nakashima-Kamimura, A.M. Wolf, T. Amo, S. Ohta, Y. Katsumata, K. Fukuda, K. Ishiwata, M. Suematsu, T. Adachi, Caloric restriction primes mitochondria for ischemic stress by deacetylating specific mitochondrial proteins of the electron transport chain, Circ. Res. 109 (2011) 396–406.
[161] C.F. Lee, J.D. Chavez, L. Garcia-Menendez, Y. Choi, N.D. Roe, Y.A. Chiao, J.S. Edgar, Y.A. Goo, D.R. Goodlett, J.E. Bruce, R. Tian, Normalization of NAD(+) redox balance as a therapy for heart failure, Circulation 134 (2016) 883–894.
[162] K.A. Hershberger, A.S. Martin, M.D. Hirschey, Role of NAD(+) and mitochondrial sirtuins in cardiac and renal diseases, Nat. Rev. Nephrol. 13 (2017) 213–225.
[163] R. de Cabo, D. Carmona-Gutierrez, M. Bernier, M.N. Hall, F. Madeo, The search for antiaging interventions: from elixirs to fasting regimens, Cell 157 (2014) 1515–1526.
[164] C. Canto, R.H. Houtkooper, E. Pirinen, D.Y. Youn, M.H. Oosterveer, Y. Cen, P.J. Fernandez-Marcos, H. Yamamoto, P.A. Andreux, P. Cettour-Rose, K. Gademann, C. Rinsch, K. Schoonjans, A.A. Sauve, J. Auwerx, The NAD(+) precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity, Cell Metab. 15 (2012) 838–847.
[165] J. Ren, Y. Zhang, Targeting autophagy in aging and aging-related cardiovascular diseases, Trends Pharmacol. Sci. 39 (2018) 1064–1076.
[166] K.T. Howitz, K.J. Bitterman, H.Y. Cohen, D.W. Lamming, S. Lavu, J.G. Wood, R.E. Zipkin, P. Chung, A. Kisielewski, L.L. Zhang, B. Scherer, D.A. Sinclair, Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan, Nature 425 (2003) 191–196.
[167] J.A. Baur, D.A. Sinclair, Therapeutic potential of resveratrol: the in vivo evidence, Nat. Rev. Drug Discov. 5 (2006) 493–506.
[168] J.H. Bauer, S. Goupil, G. Garber, S.L. Helfand, An accelerated assay for the identification of lifespan-extending interventions in *Drosophila melanogaster*, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 12980–12985.
[169] M.H. Arafa, N.S. Mohammad, H.H. Atteia, H.R. Abd-Elaziz, Protective effect of resveratrol against doxorubicin-induced cardiac toxicity and fibrosis in male experimental rats, J. Physiol. Biochem. 70 (2014) 701–711.
[170] J.A. Mattison, M. Wang, M. Bernier, J. Zhang, S.S. Park, S. Maudsley, S.S. An, L. Santhanam, B. Martin, S. Faulkner, C. Morrell, J.A. Baur, L. Peshkin, D. Sosnowska, A. Csiszar, R.L. Herbert, E.M. Tilmont, Z. Ungvari, K.J. Pearson, E.G. Lakatta, R. de Cabo, Resveratrol prevents high fat/sucrose diet-induced central arterial wall inflammation and stiffening in nonhuman primates, Cell Metab. 20 (2014) 183–190.
[171] T. Finkel, The metabolic regulation of aging, Nat. Med. 21 (2015) 1416–1423.
[172] E.R. Olson, J.E. Naugle, X. Zhang, J.A. Bomser, J.G. Meszaros, Inhibition of cardiac fibroblast proliferation and myofibroblast differentiation by resveratrol, Am. J. Physiol. Heart Circ. Physiol. 288 (2005) H1131–H1138.
[173] N.L. Price, A.P. Gomes, A.J. Ling, F.V. Duarte, A. Martin-Montalvo, B.J. North, B. Agarwal, L. Ye, G. Ramadori, J.S. Teodoro, B.P. Hubbard, A.T. Varela, J.G. Davis, B. Varamini, A. Hafner, R. Moaddel, A.P. Rolo, R. Coppari, C.M. Palmeira, R. de Cabo, J.A. Baur, D.A. Sinclair, SIRT1 is required for AMPK activation and the beneficial effects of resveratrol on mitochondrial function, Cell Metab. 15 (2012) 675–690.
[174] V.B. Pillai, N.R. Sundaresan, G. Kim, M. Gupta, S.B. Rajamohan, J.B. Pillai, S. Samant, P.V. Ravindra, A. Isbatan, M.P. Gupta, Exogenous NAD blocks cardiac hypertrophic response via activation of the SIRT3-LKB1-AMP-activated kinase pathway, J. Biol. Chem. 285 (2010) 3133–3144.
[175] T. Chen, J. Li, J. Liu, N. Li, S. Wang, H. Liu, M. Zeng, Y. Zhang, P. Bu, Activation of SIRT3 by resveratrol ameliorates cardiac fibrosis and improves cardiac function via the TGF-beta/Smad3 pathway, Am. J. Physiol. Heart Circ. Physiol. 308 (2015) H424–H434.
[176] S. Mukherjee, D. Ray, I. Lekli, I. Bak, A. Tosaki, D.K. Das, Effects of Longevinex (modified resveratrol) on cardioprotection and its mechanisms of action, Can. J. Physiol. Pharmacol. 88 (2010) 1017–1025.
[177] S. Frojdo, D. Cozzone, H. Vidal, L. Pirola, Resveratrol is a class IA phosphoinositide 3-kinase inhibitor, Biochem. J. 406 (2007) 511–518.
[178] A. Martin-Montalvo, E.M. Mercken, S.J. Mitchell, H.H. Palacios, P.L. Mote, M. Scheibye-Knudsen, A.P. Gomes, T.M. Ward, R.K. Minor, M.J. Blouin, M. Schwab, M. Pollak, Y. Zhang, Y. Yu, K.G. Becker, V.A. Bohr, D.K. Ingram, D.A. Sinclair, N.S. Wolf, S.R. Spindler, M. Bernier, R. de Cabo, Metformin improves healthspan and lifespan in mice, Nat. Commun. 4 (2013) 2192.
[179] E. Dazert, M.N. Hall, mTOR signaling in disease, Curr. Opin. Cell Biol. 23 (2011) 744–755.
[180] W. De Haes, L. Frooninckx, R. Van Assche, A. Smolders, G. Depuydt, J. Billen, B.P. Braeckman, L. Schoofs, L. Temmerman, Metformin promotes lifespan through mitohormesis via the peroxiredoxin PRDX-2, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) E2501–E2509.
[181] H. Xiao, X. Ma, W. Feng, Y. Fu, Z. Lu, M. Xu, Q. Shen, Y. Zhu, Y. Zhang, Metformin attenuates cardiac fibrosis by inhibiting the TGFbeta1-Smad3 signalling pathway, Cardiovasc. Res. 87 (2010) 504–513.
[182] L.M. Berstein, Metformin in obesity, cancer and aging: addressing controversies, Aging (Albany NY) 4 (2012) 320–329.
[183] H. Sasaki, H. Asanuma, M. Fujita, H. Takahama, M. Wakeno, S. Ito, A. Ogai, M. Asakura, J. Kim, T. Minamino, S. Takashima, S. Sanada, M. Sugimachi, K. Komamura, N. Mochizuki, M. Kitakaze, Metformin prevents progression of heart failure in dogs: role of AMP-activated protein kinase, Circulation 119 (2009) 2568–2577.
[184] I. Tzoulaki, M. Molokhia, V. Curcin, M.P. Little, C. Millett, A. Ng, R.I. Hughes, K. Khunti, M.R. Wilkins, A. Majeed, P. Elliott, Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database, BMJ 339 (2009) b4731.
[185] T.K. Schramm, G.H. Gislason, A. Vaag, J.N. Rasmussen, F. Folke, M.L. Hansen, E.L. Fosbol, L. Kober, M.L. Norgaard, M. Madsen, P.R. Hansen, C. Torp-Pedersen, Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study, Eur. Heart J. 32 (2011) 1900–1908.
[186] Y.S. Lee, W.S. Kim, K.H. Kim, M.J. Yoon, H.J. Cho, Y. Shen, J.M. Ye, C.H. Lee, W.K. Oh, C.T. Kim, C. Hohnen-Behrens, A. Gosby, E.W. Kraegen, D.E. James, J.B. Kim, Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states, Diabetes 55 (2006) 2256–2264.
[187] M. Li, Y. Zhang, Y. Yu, S. Yang, J. Iqbal, Q. Mi, B. Li, Z. Wang, W. Mao, H. Xie, S. Chen, Berberine improves pressure overload-induced cardiac hypertrophy and dysfunction through enhanced autophagy, Eur. J. Pharmacol. 728 (2014) 67–76.
[188] Y. Zhang, S. Yang, M. Li, J. Iqbal, C.V. Bourantas, Q. Mi, Y. Yu, J. Li, S. Zhao, N. Tian, S. Chen, Berberine attenuates adverse left ventricular remodeling and cardiac dysfunction after acute myocardial infarction in rats: role of autophagy, Clin. Exp. Pharmacol. Physiol. 41 (2014) 995–1002.
[189] X. Han, H. Tai, X. Wang, Z. Wang, J. Zhou, X. Wei, Y. Ding, H. Gong, C. Mo, J. Zhang, J. Qin, Y. Ma, N. Huang, R. Xiang, H. Xiao, AMPK activation protects cells from oxidative stress-induced senescence via autophagic flux restoration and intracellular NAD(+) elevation, Aging Cell 15 (2016) 416–427.
[190] Z. Zhang, X. Li, F. Li, L. An, Berberine alleviates postoperative cognitive dysfunction by suppressing neuroinflammation in aged mice, Int. Immunopharmacol. 38 (2016) 426–433.
[191] Y. Yu, Y. Zhao, F. Teng, J. Li, Y. Guan, J. Xu, X. Lv, F. Guan, M. Zhang, L. Chen, Berberine improves cognitive deficiency and muscular dysfunction via activation of the AMPK/SIRT1/PGC-1α pathway in skeletal muscle from naturally aging rats, J. Nutr. Health Aging 22 (2018) 710–717.
[192] Y. Hong, S. Hui, T. Chan, J.Y. Hou, Effect of berberine on regression of pressure-overload induced cardiac hypertrophy in rats, Am. J. Chin. Med. 30 (2002) 589–599.
[193] X. Zeng, X. Zeng, Y.Y. Li, Efficacy and safety of berberine for congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy, Am. J. Cardiol. 92 (2003) 173–176.
[194] I. Bjedov, L. Partridge, A longer and healthier life with TOR down-regulation: genetics and drugs, Biochem. Soc. Trans. 39 (2011) 460–465.
[195] P. Kapahi, B.M. Zid, T. Harper, D. Koslover, V. Sapin, S. Benzer, Regulation of lifespan in *Drosophila* by modulation of genes in the TOR signaling pathway, Curr. Biol. 14 (2004) 885–890.
[196] D.E. Harrison, R. Strong, Z.D. Sharp, J.F. Nelson, C.M. Astle, K. Flurkey, N.L. Nadon, J.E. Wilkinson, K. Frenkel, C.S. Carter, M. Pahor, M.A. Javors, E. Fernandez, R.A. Miller, Rapamycin fed late in life extends lifespan in genetically heterogeneous mice, Nature 460 (2009) 392–395.
[197] R.A. Miller, D.E. Harrison, C.M. Astle, J.A. Baur, A.R. Boyd, R. de Cabo, E. Fernandez, K. Flurkey, M.A. Javors, J.F. Nelson, C.J. Orihuela, S. Pletcher, Z.D. Sharp, D. Sinclair, J.W. Starnes, J.E. Wilkinson, N.L. Nadon, R. Strong,

Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice, J. Gerontol. A Biol. Sci. Med. Sci. 66 (2011) 191–201.
[198] D.F. Dai, P.P. Karunadharma, Y.A. Chiao, N. Basisty, D. Crispin, E.J. Hsieh, T. Chen, H. Gu, D. Djukovic, D. Raftery, R. Beyer, M. MacCoss, P.S. Rabinovitch, Altered proteome turnover and remodeling by short-term caloric restriction or rapamycin rejuvenate the aging heart, Aging Cell 13 (2014) 529–539.
[199] Y.A. Chiao, P.S. Rabinovitch, The aging heart, Cold Spring Harb. Perspect. Med. 5 (2015) a025148.
[200] F. Neff, D. Flores-Dominguez, D.R. Ryan, M. Horsch, S. Schroder, T. Adler, L.C. Afonso, J.A. Aguilar-Pimentel, L. Becker, L. Garrett, W. Hans, M.M. Hettich, R. Holtmeier, S.M. Holter, K. Moreth, C. Prehn, O. Puk, I. Racz, B. Rathkolb, J. Rozman, B. Naton, R. Ordemann, J. Adamski, J. Beckers, R. Bekeredjian, D.H. Busch, G. Ehninger, J. Graw, H. Hofler, M. Klingenspor, T. Klopstock, M. Ollert, J. Stypmann, E. Wolf, W. Wurst, A. Zimmer, H. Fuchs, V. Gailus-Durner, M.H. de Angelis, D. Ehninger, Rapamycin extends murine lifespan but has limited effects on aging, J. Clin. Invest. 123 (2013) 3272–3291.