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Aging and Autophagy in the Heart

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Abstract

The aging population is increasing in developed countries. Since the incidence of cardiac disease increases dramatically with age, it is important to understand the molecular mechanisms through which the heart becomes either more or less susceptible to stress. Cardiac aging is characterized by the presence of hypertrophy, fibrosis, and accumulation of misfolded proteins and dysfunctional mitochondria. Macroautophagy (hereafter referred to as “autophagy”) is a lysosome-dependent bulk degradation mechanism that is essential for intracellular protein and organelle quality control. Autophagy and autophagic flux are generally decreased in aging hearts, and murine autophagy loss-of-function models develop exacerbated cardiac dysfunction that is accompanied by accumulation of misfolded proteins and dysfunctional organelles. On the other hand, stimulation of autophagy generally improves cardiac function in mouse models of protein aggregation by removing accumulated misfolded proteins, dysfunctional mitochondria, and damaged DNA, thereby improving the overall cellular environment and alleviating aging-associated pathology in the heart. Increasing lines of evidence suggest that autophagy is required for many mechanisms that mediate lifespan extension, such as caloric restriction, in various organisms. These results raise the exciting possibility that autophagy may play an important role in combating the adverse effects of aging in the heart. In this review, we discuss the role of autophagy in the heart during aging, how autophagy alleviates age-dependent changes in the heart, and how the level of autophagy in the aging heart can be restored.

Keywords

Aging; autophagy; oxidative stress; mitochondria; mitophagy; protein acetylation; mitochondrial unfolded protein response; NAD+

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Disclosures

None.

Subject Terms

Aging; Cell Signaling/Signal Transduction; Myocardial Biology; Metabolism

The incidence of cardiovascular disease progressively increases with age in both men (from 10 per 1000 people at 45–54 years of age to 74 per 1000 people at 85–94 years of age) and women (from 4 to 65 per 1000 for the comparable age groups) [1]. Despite recent progress in cardiovascular treatment, the total prevalence of age-related diseases, including cardiovascular diseases (CVD), is still increasing [2]. High blood pressure, obesity, and metabolic syndrome increase with age, and these conditions facilitate the development of heart disease, which is a major cause of chronic disability, morbidity and mortality in the elderly [3, 4].

Examination of the cell biology of the aging process has revealed that it is often associated with dysfunctional organelles, which trigger oxidative stress, protein misfolding, and cell death, and induce precipitous declines in the maintenance of cellular quality control mechanisms [5–7]. In particular, an important pathological feature of aging is the development of mitochondrial abnormalities, where reactive oxygen species (ROS) progressively accumulate during aging as a result of damage to mitochondrial proteins, an imbalance between oxidative stress and anti-oxidant mechanisms, and increases in electron leakage from dysfunctional electron transport chains [8–12]. Accumulation of ROS induces mutations in mitochondrial DNA (mtDNA) and impedes the tricarboxylic acid cycle and electron transport chain complexes, thereby attenuating the bioenergetic function of mitochondria. This causes a vicious cycle that progressively aggravates oxidative stress and mitochondrial dysfunction [10–12]. Prevention of these aging-associated catastrophes requires properly functioning quality control mechanisms that allow elimination and well-coordinated replenishment of damaged proteins and organelles. Cardiomyocytes in the adult heart appear to retain the ability to divide in response to stress, but their proliferation is very inefficient. The adult heart is thus greatly reliant on the cellular quality control mechanisms, since damaged proteins and organelles cannot be easily diluted through cell division [13, 14]. Autophagy is an evolutionarily conserved mechanism that targets damaged or long-lived proteins and organelles for degradation through lysosomes [15, 16]. Autophagy can be either non-selective or cargo-specific, and mitochondrial-specific autophagy is referred to as mitophagy. Accumulating lines of evidence support a crucial role for autophagy and mitophagy in the regulation of cardiac homeostasis at baseline and in response to stress [15, 17, 18], and their downregulation appears to contribute to the aging process [16, 19, 20] in many organs. This review will summarize the current understanding of the role of autophagy in the regulation of aging in the heart. Readers are also referred to recent reviews on similar topics with distinct focuses, such as longevity and metabolism, in order to better understand the broader functions of autophagy [16, 21].

2. Manifestation of aging in the heart

Aging hearts exhibit unique histological and biochemical features [22–25]. Increases in apoptosis and necrosis, proliferation of myocyte nuclei, increased myocyte volume, and

connective tissue accumulation are frequently observed in the myocardium of old animals [26–28]. Senescence-associated ectopic β-galactosidase activity and dense bodies with autofluorescence, consisting of damaged proteins and lipid accumulates, called lipofuscin [29], are also increased. In addition, aging affects the abundance of some molecules, including the tumor suppressors $p16^{INK4}$ and $p19^{ARF}$ [30, 31]. How do these changes affect cardiac function and susceptibility to heart failure in the elderly? Aging cardiomyocytes are less capable of undergoing compensatory hypertrophy and proliferation in response to increased workload [22, 32–35]. As a result, aging increases wall stress that is not normalized by ventricular remodeling [36]. Furthermore, induction of cell protective mechanisms, such as expression of anti-oxidant and heat shock proteins, in response to pathologic insults is attenuated in aging hearts [33, 37, 38]. Optimal therapeutic interventions to alleviate the adverse effects of aging should prevent cell death and accumulation of senescent myocytes [22]. For example, A2E, a major component of toxic lipofuscin, upregulates inflammatory cytokines and chemokines and contributes to the inflammatory response in aging tissues, but activation of autophagy appears to protect the tissue by eliminating both toxic aggregates and activation of inflammation [39]. As we discuss later, however, autophagy and autophagic flux are generally downregulated in the aging heart.

3. Molecular mechanisms of aging in the heart

Since aging increases the risk of diseases and reduces organ function, elucidation of the mechanisms that serve to counteract the adverse effects of aging has significant clinical implications [40]. Evolutionarily conserved defined molecular mechanisms are involved in the regulation of lifespan in animals [40–43], and activation of these mechanisms may affect the aging of individual organs and the cells therein. Aging is a multifunctional process, with many mechanisms contributing to functional decline in organs and tissues. Accumulation of damaged proteins and mitochondria is commonly observed in aged cells. In addition, production of ROS in various organs is progressively enhanced over the years and oxidative stress accumulates during the aging process [10, 12]. Likewise, increased ROS and accumulation of damaged proteins and organelles in the heart also occur in the presence of high blood pressure and metabolic abnormality, which facilitate senescence in the heart [44, 45].

ROS progressively accumulate during aging, due to both electron leakage from mitochondria resulting from impaired mitochondrial oxidative phosphorylation and an imbalance between the expression of ROS-producing enzymes and anti-oxidant proteins [10, 46]. The accumulated ROS further promote the mtDNA mutations and deletions that accumulate over time, leading to a progressive reduction in mtDNA content [47]. ROS can also impair the enzymes involved in oxidative phosphorylation, particularly those containing an iron-sulfur cluster [48]. Finally, oxidative stress is associated with mitochondrial permeability transition pore opening, which promotes necrosis and cell death in mammalian cells [49]. Mitochondrial dysfunction is a common feature of the aging process [50], and systemic mitochondrial overexpression of catalase extends lifespan and delays the aging process in mice [51]. These observations suggest that accumulation of ROS in mitochondria contributes to the aging process in mammals [52].

In addition to electron leakage from the electron transport chain, mitochondrial expression of Nox4, a major intracellular isoform of NADPH oxidase in the heart, is upregulated in the aged heart, contributing to ROS production and the development of cardiac abnormalities in aging mice [53]. Nox4 is upregulated by pressure overload through an NF-κB-dependent mechanism [54] but the mechanism by which Nox4 is upregulated in the aging heart is currently unknown. It would be interesting to test whether the increased susceptibility of aging hearts to stress is alleviated in cardiac-specific Nox4 knock-out mice [55]. However, it should be noted that endogenous Nox4 also possesses physiological functions, such as induction of angiogenesis [56] and autophagy in response to glucose deprivation [57] in cardiomyocytes. Thus, further investigation is required to fully elucidate the role of ROS in the overall responses of the heart during aging.

Mitochondrial stress triggers a series of events, including damage to proteins [58] and mtDNA [59], activation of mitochondrial mechanisms of degradation of both individual proteins [60] and partial or whole organelles [61], and mitochondrial biogenesis [62], thereby causing a condition in which misfolded proteins accumulate or there is a mismatch between mtDNA-encoded proteins and nuclear-encoded proteins. This condition activates a set of adaptive responses collectively termed the mitochondrial unfolded protein response (UPR^{mt}) [63], including activation of chaperones and other mitochondrial quality control mechanisms such as mitophagy [64]. The UPR^{mt} is essential for long-term maintenance of mitochondrial quality and affects many mechanisms known to influence either lifespan or aging [60]. Although the UPR^{mt} is evolutionarily conserved and has been studied extensively in *Caenorhabditis elegans*, the detailed signaling mechanisms found in mammalian cells are poorly understood. Elucidating the molecular mechanisms by which the UPR^{mt} maintains mitochondrial homeostasis and whether the UPR^{mt} acts through autophagy and/or mitophagy in mammalian cardiomyocytes would be interesting and should provide clues for the development of novel interventions to achieve anti-senescence therapy in the heart. It should be noted that endoplasmic reticulum (ER) stress also induces autophagy and a UPR to eliminate misfolded proteins and defective organelles [65]. However, the connection between ER stress and aging is, to date, less well defined than that between the UPR^{mt} and aging.

Increases in oxidative stress induce DNA damage, which, in turn, either induces a series of DNA repair mechanisms or activates either cell death or cellular senescence mechanisms. Increases in DNA damage and defective DNA repair have been shown to inhibit autophagy [66, 67]. Somatic mtDNA mutation inhibits autophagy, thereby allowing mutated mtDNA to escape degradation and promote mitochondrial dysfunction. When DNA damage induces senescence, it is accompanied by a unique phenotype, called the “senescence-associated secretory phenotype” (SASP) [68], that mediates chronic inflammation, thereby further promoting DNA damage and senescence. DNA damage-induced cellular senescence stabilizes GATA4, thereby inducing SASP through activation of NF-κB. Interestingly, p62-mediated selective autophagy degrades GATA4, whereas GATA4 is stabilized in human fetal lung fibroblasts undergoing senescence due to suppression of autophagy [69]. These observations suggest that autophagy may inhibit the adverse effects of aging by negatively regulating SASP and aging-associated inflammation.

Telomeres are regions of repetitive nucleotide sequences located at the ends of chromosomes that protect the chromosomal end structures from damage. Each time cells divide, the telomere ends become shorter. Since telomere shortening causes senescence through activation of the p53 and Rb pathways, the molecular mechanism controlling telomere length is intimately connected to aging [70]. Although cardiomyocytes in the adult heart rarely proliferate, telomere damage is also caused by oxidative stress, which, in turn, activates signaling mechanisms leading to senescence [70]. Importantly, the health of the heart is dependent upon basal turnover of cardiomyocytes generated from cardiac progenitor cells. Telomere attrition and DNA damage induce senescence in cardiac progenitors, resulting in a loss of regenerative capacity and promotion of cardiac senescence [71]. It has recently been shown that quiescent satellite cells in skeletal muscles are capable of maintaining their stemness by activating autophagy [72]. However, autophagy is attenuated in aged satellite cells, leading to stimulation of senescence through accumulation of oxidative stress and damaged proteins and organelles [72].

Another important mechanism regulating senescence is protein acetylation, which is regulated by a balance between protein acetylases and deacetylases. Spermidine, an acetyltransferase inhibitor, prolongs the lifespan of yeast, flies, and nematodes in an autophagy-dependent fashion, by inhibiting protein acetylation of cytoplasmic and nuclear proteins [73]. In addition, the sirtuin family of protein deacetylases is particularly relevant in the regulation of lifespan and aging. Sirtuins are a family of seven NAD+-dependent protein deacetylases known to be involved throughout the evolutionary tree in lifespan extension in response to caloric restriction (CR) and resveratrol, a naturally occurring polyphenol that stimulates Sirt1. The Sirt1 isoform acts in both the nucleus and the cytoplasm [74], and its expression increases in the aging heart, most likely as a compensatory mechanism [75, 76]. Sirt1 can retard senescence and confer resistance to oxidative stress in the heart [75], and promotes autophagy through deacetylation and stimulation of FoxO1 in cardiomyocytes [77]. Sirt1 negatively regulates p66shc expression in human umbilical vein endothelial cells [78]. p66shc is a multifunctional adapter protein and its deletion prolongs lifespan in mice [79]. p66shc positively regulates oxidative stress by stimulating mitochondrial oxidative phosphorylation and downregulating FoxO-mediated protection against oxidative stress [80–82]. Sirt3, a mitochondrial sirtuin isoform, can stimulate oxidative phosphorylation by directly deacetylating the electron transport chain complexes [83]. Sirt3 also inhibits pathological cardiac hypertrophy by deacetylating cyclophilin D, a protein that regulates mitochondrial permeability transition pore opening and prevents the adverse effects of aging in the heart [84, 85].

Mammalian target of rapamycin (mTOR), a serine threonine kinase that regulates protein synthesis, transcription of mitochondrial proteins and autophagy, has also been implicated in the regulation of lifespan and aging [86]. mTOR suppresses autophagy through phosphorylation of Ulk1, primarily through activation of mTOR complex 1 (mTORC1) [87]. mTOR has drawn particular attention in the area of aging because the mTOR inhibitor rapamycin has been shown to increase lifespan in mammals [88]. A recent report showed that the activity of mTOR does not increase with age in C57BL/6J mice [89]. Although these findings suggest that endogenous mTOR may not be directly involved in the aging process,

they nonetheless do not exclude the possibility that the beneficial effects of rapamycin treatment on lifespan are mediated through suppression of endogenous mTOR.

A recent study found that serum levels of GDF11, a member of the TGF-β superfamily of cytokines, decrease with age in mice and that restoring the level of GDF11 decreases aging-associated cardiac phenotypes, including cardiac hypertrophy [90]. Although the age-dependent decrease in GDF11 and its effect upon aging-induced cardiac hypertrophy could not be reproduced in another report [91], the anti-senescence effect of GDF11 was also observed in skeletal muscles [92]. Furthermore, systemic supplementation of GDF11 was shown to increase the LC3-II/LC3-I ratio in skeletal muscle. However, whether GDF11 increases autophagic flux or whether autophagy plays a causative role in mediating the anti-senescence effect of GDF11 was not tested in this study.

Taken together, these studies show that the list of potential mechanisms controlling senescence of the organism as a whole and of individual organs such as the heart is growing. According to the hormesis hypothesis, the accumulation of molecular mechanisms conferring stress resistance may prevent senescence of organisms. Thus, it would be interesting to investigate whether the aforementioned mechanisms controlling senescence protect the heart against stress and inhibit accumulation of damage in the heart. Interestingly, as described below, these mechanisms generally affect autophagy.

4. The role of autophagy during aging of the heart

Damage to proteins, DNA and cellular organelles plays an important role in aging [93]. Accumulation of damaged proteins and organelles leads to the age-associated malfunction of many biological processes. Thus, reduced degradation of proteins and organelles may contribute to the aging process [29]. In cardiomyocytes, the accumulation of dysfunctional organelles and toxic proteins results in global cardiac dysfunction. Since autophagy plays a crucial role in the degradation of long-lived proteins and organelles, it is an essential mechanism for maintenance of tissue homeostasis in the heart during the aging process [15, 16, 94]. Three types of autophagy have been identified: microautophagy, chaperone-mediated autophagy (CMA), and macroautophagy. In microautophagy, cytoplasmic cargo is directly trapped and engulfed through membrane invagination by lysosomes. Although it is believed to be a random process, recent evidence suggests that parts of mitochondria are also degraded through this mechanism [95]. CMA, on the other hand, specifically degrades cytosolic proteins with a KFERQ motif, by directly transferring them to lysosomes. In macroautophagy, hereafter referred to as autophagy, small vesicular sacs, called isolation membranes or phagophores, are initially formed. The phagophores enclose cytosolic long-lived proteins and organelles, resulting in the formation of double-membraned structures called autophagosomes. The autophagosomes then fuse with lysosomes, which leads to the degradation of the sequestered cellular contents through digestion of the cargo by lysosomal hydrolases [15, 16, 94]. Essentially nothing is known regarding the role of microautophagy and CMA during aging in the heart. Thus, we focus on macroautophagy in the discussion below.

4.1 Autophagy is downregulated during the course of aging

Autophagy is downregulated in the heart during the course of aging [96]. The general mechanisms of aging described above may also contribute to this downregulation of autophagy (Figure 1). Seemingly paradoxically, although ROS and misfolded proteins can stimulate autophagy, suppression of autophagy is commonly observed in aging hearts with increased oxidative stress, misfolded proteins, and dysfunctional mitochondria. One possible explanation for this apparent paradox is that continuous activation of autophagy due to higher oxidative stress and protein misfolding may lead to exhaustion of the autophagic machinery, eventually causing suppression of autophagy. A similar phenomenon, termed "autophagy exhaustion", was reported to have been observed following HIV-1 infection [97]. Aging is also characterized by attenuation of stress-induced adaptations, which may result, in part, from the suppression of autophagy. In particular, activation of autophagy is required to potentiate the protective effect of ischemic preconditioning [98], raising the possibility that autophagy exhaustion may contribute to the increased susceptibility of elderly patients to myocardial ischemia. Whether autophagy exhaustion actually takes place in aging hearts remains to be tested.

Activation of major suppressors of autophagy, such as Mst1 [99] and mTOR [100], or suppression of major activators of autophagy, such as Sirt1 [77], may also cause downregulation of autophagy in the heart. Further experimentation is required to test these hypotheses.

In addition, a variety of other mechanisms have been shown to contribute to the age-dependent downregulation of autophagy. The genes involved in general and mitochondria-specific autophagy are regulated by transcription factors, including FoxO, HIF-1, p53, E2F1, NF-κB, KLF4, TFEB, and ZKSCAN3 [77101102]. The transcriptional activity of FoxO is negatively regulated by Akt-mediated phosphorylation and by lysine acetylation resulting from decreases in NAD+ and consequent inactivation of Sirt1 in the heart. This, in turn, may contribute to decreased expression of autophagy-related genes in the aged heart. Aging has also been shown to upregulate miR-216a, which, in turn, downregulates Beclin1, thereby inhibiting ox-LDL-induced stimulation of autophagy in endothelial cells [103]. In contrast, atrogin-1, an E3 uibiquitin ligase known to be activated in response to muscle atrophy, induces autophagy through degradation of charged multivesicular body protein 2B, a component of the endosomal sorting protein complex that is essential for autophagy [104]. However, although the activity of the ubiquitin proteasome system (UPS) declines with aging, whether atrogin-1 is downregulated in aging hearts is unknown. Finally, saturated and unsaturated fatty acids induce metabolomic profiles that differentially affect aging through activation of distinct forms of autophagy in the liver: the former activates PIK3C3- and Beclin1-dependent autophagy by depleting autophagy-inhibitory amino acids, whereas the latter activates PIK3C3- and Beclin1-independent autophagy by increasing the level of NAD +. Whereas the effects of saturated fatty acids on health are detrimental, those of unsaturated fatty acids are beneficial [105]. However, how the metabolic perturbation observed in age-associated heart disease affects metabolomic profiles and autophagy remains to be elucidated.

4.2 Autophagy is essential for preventing aging in the heart

Increasing lines of evidence suggest that autophagy is intimately involved in the regulation of lifespan and aging (Reviewed in [21]). Loss-of-function mutations in Atg1, Atg7, Atg18 and Beclin1, key autophagy genes, decrease the lifespan of the nematode *C. elegans* [106]. Similarly, in a genetic screen of budding yeast, several short-lived mutants had autophagy defects, including 10 ATG mutations found among a total of 117 short-lived mutants [107]. Deficient expression of Atg1 facilitates accumulation of ROS and muscle degeneration, mimicking the aging phenotype, in the fruit fly *Drosophila melanogaster* [108]. Mutations in Atg8 also induce accumulation of insoluble proteins, increase sensitivity to ROS and shorten lifespan in *Drosophila*, whereas increased expression of Atg8 in the nervous system of *Drosophila* extends its lifespan [109]. Autophagy-related genes have also been shown to promote survival in worms and flies exposed to prolonged starvation [110], by alleviating age-associated pathologies, including mitochondrial and cardiac dysfunction [108].

In mammals, tissue-specific knockout of ATG genes induces multiple age-associated symptoms, including accumulation of intracellular inclusion bodies containing ubiquitinylated proteins, accumulation of lysosomes containing lipofuscin, disorganized mitochondria, and protein oxidation [111–115]. In contrast, adenovirus-directed overexpression of Atg7 that corrected a hepatic autophagic defect was shown to diminish ER stress and counteract insulin resistance [115]. Stimulation of autophagy reduces oncogenesis, maintains neuronal function [116], improves immune responses [117], reduces inflammation [118], and improves lipid mobilization [119] in the organism as a whole, thereby improving overall fitness during aging [16, 21]. However, more studies may be needed to clarify whether the lifespan of mice can be prolonged by selectively correcting aging-associated defects in autophagy.

Autophagy may be especially important in non-proliferating cells since there is no dilution of toxic materials accumulated during aging through cell division. In terms of cardiac aging, mice in which the Atg5 protein is cardiac-specifically deleted through constitutive αMHC-Cre expression develop dilated cardiomyopathy with severe systolic dysfunction during aging, accompanied by sarcomeric disarray and accumulation of dysfunctional and abnormal mitochondria [96]. Cardiac-specific deletion of GSK-3α also promoted the development of cardiac aging, and this was accompanied by suppression of autophagy [120]. One cautionary note is that the use of αMHC-Cre, originally generated by Dr. Michael Schneider's laboratory for use in aging studies, may potentially be problematic since cardiac-specific Cre alone induces significant time-dependent cardiac dysfunction [121]. Nevertheless, these results strongly suggest that autophagy is required for cardiac homeostasis during aging and that downregulation of autophagy contributes to cardiac pathology during aging. Indeed, a genome-wide association study of aging identified a SNP near the Atg4c gene as being associated with a higher risk of death, suggesting that autophagy may be intimately involved in the risk of heart disease in elderly patients [122]. Furthermore, autophagy also alleviates accumulation of advanced glycation end products (AGEs) [123] and preamyloid oligomers [124]. However, determining whether or not downregulation of autophagy mechanistically contributes to the development of cardiac aging awaits further experimentation to test whether restoring the level of autophagy rescues the aging phenotype.

The lysosome-associated membrane protein 2a (LAMP2a), a protein required for CMA, is also downregulated during the aging process in the mouse liver [125]. Restoration of LAMP2a prevents aging-associated defects in CMA, and decreases the abundance of oxidized proteins, polyubiquitinated protein aggregates, and apoptotic cells in the liver [125]. The role of CMA in cardiac aging remains to be elucidated.

5. The role of mitophagy

Damaged mitochondria can be eliminated through a specialized form of autophagy termed "mitophagy" or "mitochondrial autophagy". Autophagosomes containing only mitochondria have been observed in electron microscopic analyses of the hearts of adult mice, providing evidence for the existence of mitophagy in the heart [126]. The molecular mechanisms mediating mitochondrial autophagy and its functional significance in the heart have been reviewed recently [127]. In perhaps the most well-characterized mechanism of mitochondrial autophagy, depolarized mitochondria are marked by a PINK1-Parkin-Mfn2-dependent mechanism and engulfed by autophagosomes through an LC3-receptor-dependent mechanism [128]. A recent report showed that PINK1-induced phosphorylation of ubiquitin recruits LC3 receptor proteins, including NDP52 and optineurin, which in turn recruit the autophagy factors, including Ulk1, DFCP1 and WIPI1, to mitochondria [129]. However, more investigation is needed to fully elucidate how depolarized mitochondria are marked and recognized by LC3 and the involvement of Parkin-Mfn2 in this process. On the other hand, increasing lines of evidence suggest that mitochondrial autophagy can take place in a Parkin-independent manner [130] or even in the absence of Atg5/7 [131], suggesting that there are multiple mechanisms by which mitochondria may be degraded, perhaps in a stimulus-dependent fashion. In addition, mitochondria can be degraded by microautophagy and mitochondria-derived vesicles [61]. Given that mitochondrial dysfunction can develop with aging and that mitochondria are the major source of ROS in aging hearts, it is critically important to understand how mitochondrial autophagy is regulated in aging hearts (Figure 2).

It should be noted that there have been no studies quantitatively evaluating the changes in mitophagy during cardiac aging thus far. Since mitochondrial dysfunction is a common feature of cardiac aging, in theory, more mitophagy and mitochondrial autophagy should be observed, at least in the early phase of aging. In *C. elegans,* age-associated stress such as oxidative stress stimulates both mitochondrial biogenesis and mitophagy through SKN-1, a homolog of Nrf2, thereby coordinating mitochondrial turnover [132]. As noted above, thus far, most studies of mitophagy in the heart have focused on PINK1-Parkin-mediated mitophagy. One study showed that, although young Parkin knockout (KO) mice exhibit a normal cardiac phenotype, abnormal mitochondria accumulate in cardiomyocytes with age in these mice [133]. This suggests that endogenous Parkin may mediate mitophagy in aging hearts. It is unclear, however, how Parkin expression is regulated during aging. Furthermore, considering the fact that Parkin has multiple functions besides mitophagy [134], whether or not downregulation of Parkin directly promotes accumulation of abnormal mitochondria through a defect in mitophagy remains to be tested. Damaged mitochondria can be eliminated by multiple mechanisms, including mitochondrial proteases, ubiquitin proteasome-dependent mechanisms, Parkin-independent macroautophagy, a non-conventional form of autophagy,

microautophagy and mitochondria-derived vesicles (reviewed in [61]). Currently, how these mechanisms are affected by cardiac aging is unknown. In erythroid cells in which mtDNA mutation is stimulated, mitochondrial autophagy is downregulated by aging [67]. Accumulation of damaged mtDNA activates mTOR, which inhibits autophagy, thereby preventing elimination of mitochondria containing damaged mtDNA and initiating a feed-forward mechanism that causes rapid accumulation of dysfunctional mitochondria and cell death. It will be interesting to test whether similar mechanisms exist in aging hearts.

Mito-Timer is a time-sensitive fluorescent protein targeted to the mitochondrial matrix that can be used to evaluate mitochondrial age by quantifying the proportionate integration of young (green) and old (red) Mito-Timer protein [135]. Transgenic mice with cardiac-specific expression of Mito-Timer have recently been developed [136]. These mice should be useful for evaluating age-dependent changes in mitochondrial turnover. Age-associated deterioration in the mitochondrial quality control mechanisms, including decreases in mitophagy, may be indicated by a slower mitochondrial turnover rate in this animal model.

6. Relevant intracellular signaling mechanisms controlling autophagy during aging

6.1 Sirtuins

Yeast silent information regulator 2 (Sir2) is an evolutionarily conserved molecule that mediates lifespan extension in yeast and *Drosophila* in response to CR[137–139]. Sir2 is an NAD+-dependent protein deacetylase, and functions in a wide array of cellular processes, including gene silencing, rDNA recombination, lifespan extension, and DNA damage repair (reviewed in [140, 141]). Overexpression of Sir2 increases the lifespan of many organisms, including yeast, *C. elegans* and *Drosophila* [138, 142]. Recently, the concept that lifespan extension in terminally differentiated cells might depend upon mechanisms similar to those that regulate chronological lifespan in yeast has been challenged [143]. Nonetheless, we have shown that Sirt1, a mammalian ortholog of Sir2, is able to retard aging of the heart, an organ whose major component is terminally differentiated cardiomyocytes [140]. Sirt1 deacetylates p53 and the FoxO family transcription factors, thereby inhibiting apoptotic cell death in mice and humans [144–149]. Mice deficient in Sirt1exhibit developmental abnormality in the heart and only infrequently survive postnatally [150]. Sirt1 is upregulated by CR, and regulates fat metabolism by inhibiting fat cell differentiation and fat accumulation through regulation of PPAR-γ[151]. Three- to six-fold overexpression of Sirt1 attenuates aging-induced cardiac pathology, including hypertrophy, fibrosis, apoptosis, and upregulation of senescence markers, and protects the heart against oxidative stress [75]. Furthermore, endogenous Sirt1 protects the heart against ischemia/reperfusion injury, in part through deacetylation of FoxO1 and consequent upregulation of anti-oxidants [152]. Sirt1 also mediates fasting-induced deacetylation of FoxO1 in the heart, thereby stimulating autophagosome formation and autophagosome-lysosome fusion through transcriptional upregulation of Rab7 in cardiomyocytes [77]. Sirt3 mediates the effect of CR upon age-related hearing loss and oxidative stress in mice [153, 154]. Given that their functions favor longevity and cell survival, and that they are coupled with the metabolic state of cells and with autophagy, both Sirt1

and Sirt3 are attractive candidates for critically regulating cell survival in cardiomyocytes in response to stresses such as energy starvation.

6.2 NAD+ and protein acetylation

NAD+ is an electron acceptor in the mitochondrial electron transport chain and also acts as an essential substrate for NAD+-dependent enzymes, including sirtuins and PARP, a DNA repair enzyme. Cellular levels of NAD+ are regulated by the balance between synthesis through the de novo and salvage pathways and consumption through sirtuins and PARP. NAD+ in turn regulates the level of protein acetylation through regulation of sirtuins [155]. We have shown previously that nicotinamide phosphoribosyl transferase (Nampt), a key enzyme in the salvage pathway of NAD+ synthesis in cardiomyocytes, is downregulated in the heart in response to prolonged ischemia, which leads to decreases in the level of NAD+ in the heart, inhibition of autophagic flux, and consequent increases in cell death [156]. However, restoration of the NAD+ level by overexpressing Nampt restores the level of autophagy during prolonged ischemia and reduces the extent of myocardial infarction [156]. Autophagic flux is negatively affected by decreases in NAD+ during ischemia due to resultant decreases in lysosomal acidification. We hypothesize that maintaining the NAD+ level is essential for maintaining the activity of the H+ pump on the lysosomal membrane [157]. Decreases in NAD + also increase protein acetylation through suppression of sirtuins, which in turn suppresses autophagy.

The level of NAD+ decreases with age in many organs, due to downregulation of Nampt, defective circadian rhythm, oxidative stress, and accumulation of DNA damage [155]. Although the level of Nampt in the mouse heart is upregulated at 1 year of age, whether or not it is downregulated thereafter has not been shown. We speculate that, as in the case of prolonged ischemia, aging-induced decreases in NAD+ may induce lysosomal dysfunction, which in turn contributes to age-dependent increases in the susceptibility of the heart to ischemic injury. In the rate-limiting step of the salvage pathway of NAD+ synthesis, Nampt produces nicotinamide mononucleotide (NMN), which is then converted to NAD+. Exogenous supplementation of NMN increases NAD+ content in cardiomyocytes, stimulating Sirt1 and inducing deacetylation of cellular proteins, including FoxO, in the heart, which, in turn, protects the heart from ischemia/reperfusion injury [158]. This suggests that supplementation of NAD+ via its precursors, including NMN and nicotinamide riboside, may allow suppression of cardiac aging through activation of sirtuins, including Sirt1 and Sirt3, increases in protein deacetylation in the nucleus and mitochondria, and activation of autophagy.

6.3 IGF-I signaling

In lower organisms, inhibition of insulin-like growth factor (IGF-I) signaling, such as by Daf2 mutation in *C. elegans*, causes lifespan extension [159]. This is mediated by a loss of suppression of Daf16 or FoxO transcription factors, which regulate expression of anti-oxidants (MnSOD) and DNA damage repair enzymes (GADD45) [160–163]. In mammals, Ames and Snell dwarf mice lacking growth hormone/IGF-I signaling and IGF-I receptor heterozygous KO mice have longer lifespans [164, 165]. Systemic overexpression of klotho, a hormone known to inhibit insulin/IGF-I signaling also extends lifespan in mice [166]. It should

be noted, however, that whether or not inhibiting IGF-I signaling (and thus stimulating FoxOs) positively affects senescence and aging-related diseases in mammals *without* affecting normal function is not fully understood [167]. IGF-I may only produce a trade-off between current benefits to reproduction and later costs in senescence, like the relationship between inotropic agents and exacerbation of heart failure [168]. Interestingly, activation of Akt weakens cardiac adaptation to stress [169] and exacerbates the aging phenotype in the heart, effects which are accompanied by suppression of autophagy [170]. However, the specific role of Akt in cardiac aging and how autophagy affects this process are not yet known. Considering the apparent cell survival-promoting effects of the IGF-I-Akt axis, this issue appears to represent a paradox in longevity research, and will require clarification in each organ [165].

6.4 GSK-3, AMPK and mTOR

mTOR inhibits autophagy through phosphorylation of Ulk1, a mammalian ortholog of Atg1, at Ser 757 [87]. Conversely, suppression of mTORC1 by rapamycin stimulates autophagy in cardiomyocytes [100, 171]. Although inhibition of mTORC1 by rapamycin has been shown to attenuate the adverse effects of aging in the heart [172], whether the effect of mTORC1 suppression is mediated through stimulation of autophagy awaits further investigation using more specific interventions to control autophagy, since mTORC1 has a wide variety of cellular functions besides suppression of autophagy [86]. The activity of mTOR is regulated by multiple mechanisms [86]. However, negative regulation by GSK-3β and AMPK are particularly relevant with regards to aging and autophagy.

We have shown that GSK-3β stimulates autophagy through suppression of mTOR in cardiomyocytes [173]. In addition, cardiac-specific GSK-3α KO mice show significantly shorter lifespans and exacerbated cardiac aging due to suppression of autophagy [174]. Although it is currently unclear how the activities of GSK-3α and GSK-3β are regulated during the course of aging, they have been shown to be intimately involved in the growth and death of cardiomyocytes, mitochondrial permeability transition pore opening, and regulation of mTOR signaling [175]. Thus, further investigation is required to elucidate the roles of GSK-3α and GSK-3β in regulating cardiac aging and autophagy signaling.

Likewise, AMPK stimulates autophagy through suppression of mTORC1 and phosphorylation of Ulk1 [87, 176]. Metformin, an activator of AMPK, has been shown to increase lifespan in mice [177]. In addition, metformin also attenuates aging-induced cardiomyocyte contractile defects [178]. It would be interesting to investigate to what extent stimulation of autophagy contributes to the salutary effect of metformin.

6.5 Oxidative stress

Oxidative stress can either activate or inactivate autophagy in cardiomyocytes in a context-dependent manner (reviewed in [179]). We have shown previously that oxidative stress during ischemia/reperfusion in the heart stimulates autophagy by upregulating Beclin1 [180]. In addition, glucose deprivation and hypoxia activate autophagy through upregulation of Nox4 in the ER and consequent activation of PERK-dependent mechanisms [181]. Although increases in oxidative stress induce tissue damage, mitochondrial dysfunction and cell death,

whether age-dependent increases in oxidative stress suppress autophagy in the heart has not yet been clearly demonstrated.

7. How to stimulate autophagy

Since autophagy is downregulated with age and downregulation of autophagy promotes senescence of the heart, interventions to increase the level of autophagy may prevent or slow the progression of aging in the heart. Furthermore, considering the fact that cardiac aging is accompanied by accumulation of insoluble polymeric materials, such as lipofuscin, and damaged organelles, it would appear to be advantageous to have a degradation mechanism with a large capacity (Figure 3).

Interestingly, both CR[182139, 183, 184185] and suppression of mTOR [88, 186, 187], interventions that alleviate the adverse effects of aging and increase lifespan, promote autophagy in many cell types and organs, even when autophagy is suppressed by aging. Importantly, CR has been shown to reduce age-related pathologies and diseases in animals [188–190]. However, whether or not the beneficial effects of these interventions are mediated primarily through activation of autophagy in the heart requires further study.

Voluntary exercise activates autophagy by stimulating phosphorylation of Bcl-2 and its dissociation from Beclin1 [191]. Exercise leads to a reduction in protein aggregates in the heart, which is accompanied by increases in autophagic flux, but not in the UPS or UPR [192]. We speculate that the anti-senescence effect of exercise upon the heart [192] may be in part mediated through activation of autophagy and consequent amelioration of protein aggregate formation.

Toll interacting proteins interact with LC3 and ubiquitin, thereby binding to ubiquitin conjugates more tightly than p62 and effectively clearing highly aggregation-prone proteins such as huntington poly-glutamine protein [193]. Thus, an intervention that upregulates them in vivo might be effective in clearing protein aggregates associated with aging, such as preamyloid bodies and lipofuscin. A recent report shows, however, that Toll interacting protein promotes inflammation and apoptosis in the heart after myocardial infarction [194]. Thus, further investigation is needed to clarify the function of this protein in the heart.

Trehalose is a naturally occurring disaccharide that is induced in response to dehydration in plants and promotes their survival by inducing autophagy, thus fulfilling the definition of a hormetic response [195]. We have shown recently that trehalose treatment increases autophagy in the mouse heart and the cardiomyocytes therein [196]. It will be interesting to test whether trehalose also inhibits the adverse effects of aging in the heart by stimulating autophagy.

It should be noted that the interventions discussed above have multiple effects in the heart besides autophagy. Furthermore, their effects may be mediated through non-cardiac cells. For example, growth factors, miRNA and exosomes excreted from distal organs may mediate autophagy and inhibit senescence in the heart after reaching the heart through the systemic circulation [197]. Thus, where such is likely to be the case for a particular anti-senescence intervention, further investigation is needed to identify the responsible cell type and the mechanism of transmission.

8. Concluding remarks

Accumulating lines of evidence suggest that the ability of cardiomyocytes to maintain appropriate levels of autophagy may decline during aging of the heart. However, many questions remain unanswered. First, it is unclear when the level of autophagy becomes significantly altered during the course of aging in the human heart. Currently, evaluating the level of autophagy and autophagic flux is challenging in the human heart in vivo. Developing convenient and reliable methods to accurately evaluate cardiac autophagy is essential. Second, more investigation is needed to elucidate the molecular mechanism by which autophagy or mitochondrial autophagy is regulated during the course of aging in the heart. Autophagy is regulated not only at the level of autophagosome formation but also at the levels of autophagosome-lysosome fusion and lysosomal degradation. In particular, how the function of lysosomes is affected by aging requires further investigation. Third, more investigation is needed to clarify the functional role of autophagy or mitophagy during cardiac aging. Currently, none of the available molecular interventions allow purely specific modification of either autophagy or mitophagy in mammalian cells. Whether or not protein aggregates, such as accumulated lipofuscin, are causatively involved in cardiac aging has not been formally addressed. Development of a more selective intervention or improvement of the selectivity by combining multiple interventions appears essential. Fourth, it is important to clarify the molecular mechanisms by which autophagy or mitophagy regulates cardiac aging. Although autophagy is generally thought to be a non-specific mechanism of protein degradation, there is increasing evidence that some proteins may be specifically degraded through their association with LC3 receptor proteins [198]. Identification of specific targets of autophagy during aging may allow a better understanding of the molecular mechanisms of cardiac aging. Fifth, most of the investigations reported thus far focused only on autophagy in cardiomyocytes during aging. It is important to determine whether autophagy in other cell types, such as inflammatory cells, also affects cardiac aging and, if so, how these cells communicate with cardiomyocytes, such as through secretion of paracrine factors, circulating miRNA, or exosomes. Likewise, a better understanding of the function of autophagy in cardiac progenitor cells is also highly relevant for aging research in the heart. Finally, it is essential to develop more convenient and specific interventions to normalize the level of autophagy in the heart during aging.

Autophagy mediates many lifespan-extending and anti-senescence mechanisms [21]. In particular, considering the emerging importance of the UPR^{mt} as a fundamental mechanism of longevity enhancement, elucidating the connection between the UPR^{mt} and autophagy/mitophagy is of great interest [199]. Together with the recent advancement in understanding the molecular mechanisms of autophagy, investigating the role of autophagy/mitophagy during cardiac aging should eventually lead to the development of more efficient and specific interventions to slow senescence and increase stress resistance in the heart.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Nonstandard Abbreviations and Acronyms

Atg	autophagy related genes
CR	caloric restriction
CVD	cardiovascular diseases
ER	endoplasmic reticulum
FoxO	Forkhead box O
HDAC	histone deacetylase
IGF-I	insulin-like growth factor-I
KO	knockout
Lamp2	lysosome-associated membrane protein 2
mtDNA	mitochondrial DNA
mTOR	mammalian target of rapamycin
mTORC1	mTOR complex 1
NAD+	nicotinamide adenine dinucleotide
Nampt	nicotinamide phosphoribosyl transferase
NMN	nicotinamide mononucleotide
ROS	reactive oxygen species
SASP	senescence-associated secretory phenotype
SIRT	silent information regulator
UPS	ubiquitin proteasome system
UPR	unfolded protein response
UPR^{mt}	mitochondrial unfolded protein response

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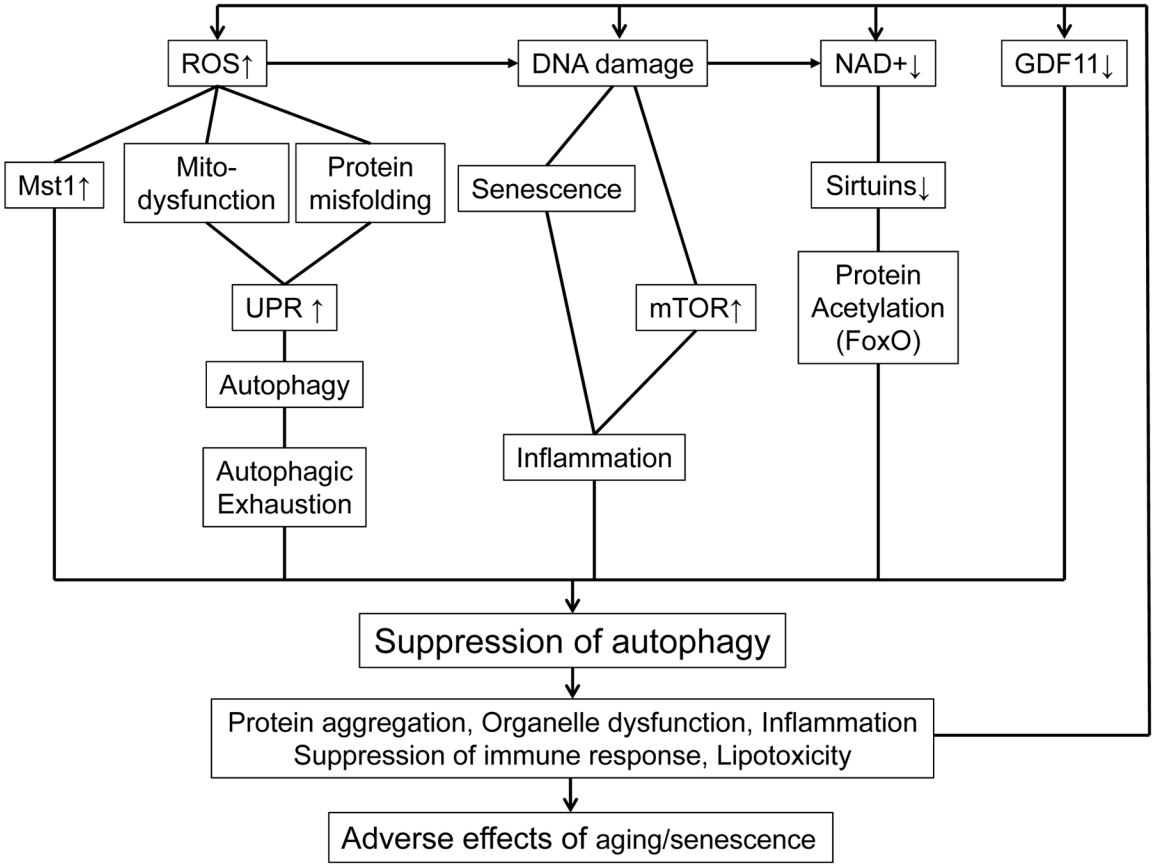

Figure 1. Regulation of cardiac aging by autophagy

Aging inhibits autophagy in cardiomyocytes through multiple mechanisms. Aging-induced suppression of autophagy induces accumulation of misfolded proteins and dysfunctional organelles, sterile infection caused by undigested mtDNA, inflammation, and lipotoxicity, thereby leading to a metabolically unhealthier environment, precipitous mitochondrial dysfunction and eventual cell death.

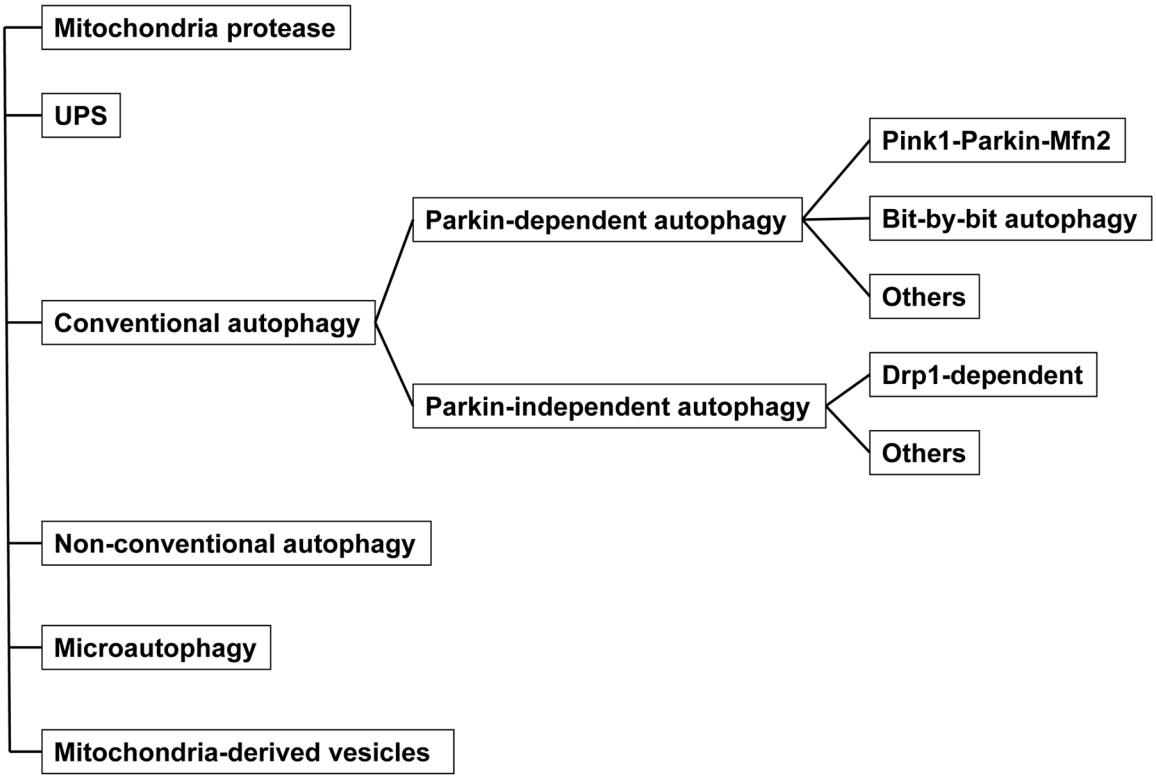

Figure 2. Mechanisms of mitochondrial autophagy in the heart

Molecular mechanisms mediating mitochondrial degradation are summarized. The contribution of each mechanism to the regulation of cardiac senescence at baseline and under stress remains to be elucidated.

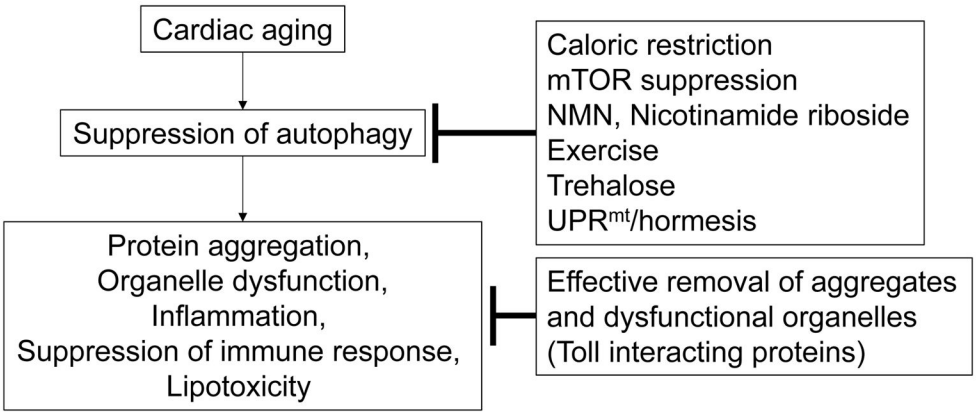

Figure 3. Possible interventions to normalize autophagy during cardiac aging

Aging inhibits autophagy and mitophagy in cardiomyocytes. Interventions to normalize autophagy and mitophagy and to alleviate protein aggregates may attenuate aging of the heart and increase the resistance of the heart stress.