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Targeting Autophagy in Aging and Aging-Related Cardiovascular Diseases

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Abstract

Aging, an irreversible biological process, serves as an independent risk factor for chronic disease including cancer, pulmonary, neurodegenerative and cardiovascular diseases. In particular, high morbidity and mortality has been associated with cardiovascular aging although effective clinical therapeutic remedy is suboptimal for the ever-rising aging population. Recent evidence suggests a unique role for aberrant aggregate clearance and protein quality control machinery - the process of autophagy in shortened lifespan, compromised healthspan, onset and development of aging-associated cardiovascular diseases. Autophagy degrades and removes long-lived or damaged cellular organelles and proteins, the functions of which decline with advanced aging. Induction of autophagy using rapamycin, resveratrol, nicotinamide derivatives, metformin, urolithin A and spermidine delays aging, prolongs lifespan and improves cardiovascular function in aging. Given the ever-rising human lifespan and aging population as well as the prevalence of cardiovascular disease provoked with increased age, it is pertinent to understand the contribution and underlying mechanisms for autophagy and organelle-selective autophagy (e.g., mitophagy) in the regulation of lifespan, healthspan and cardiovascular aging. Here we will dissect the mechanism of action for autophagy failure in aging and discuss the potential rationale of targeting autophagy using pharmacological agents as new avenues in the combat of biological and cardiovascular aging.

Keywords

Biology of aging; lifespan; autophagy; mitophagy; cardiovascular

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Biology of aging and cardiovascular sequelae of aging

Human life expectancy has gradually extended over the past several decades, contributing to a fast-growing elderly population and a high prevalence of aging-related diseases in particularly cardiovascular diseases [1, 2]. Aging is a complicated biological process, leading to progressive deterioration of cardiovascular structure and function mainly manifested as cardiac and vascular remodeling, dampened **cardiac reserve** (see Glossary) and function, endothelial defect and loss of vascular compliance [2-5]. Epidemiological evidence suggests that aging often serve as an independent risk factor for heart disease yet most of the current therapeutic strategies focus on management and prevention of the comorbidity while ignoring the nature of aging process [2]. With aging, the heart transits from a compensatory adaptive to a decompensatory maladaptive state, ultimately leading to decreased myocardial contractile capacity including increased left ventricular (LV) wall thickness and chamber dimension, altered diastolic filling pattern such as prolonged **diastole**, and impaired cardiac pump function [4, 6]. Cardiovascular aging is also featured by overt apoptosis, dampened endogenous autonomic (e.g., adrenergic) responsiveness (which stimulates cardiac contractile function), calcification and fibrosis, all of which contribute to deteriorated cardiac geometry and function [2, 3, 5, 7]. Several pathogenic factors are postulated for cardiovascular aging including oxidative stress, mitochondrial injury, genetic and epigenetic modifications, telomere shortening and metabolic dysregulation [2, 4, 8]. Among these theories, the ‘free radical theory of aging’ considers buildup of oxygen-derived free radical species as the main drive force for biological aging [2, 3]. This theory receives validation of lifespan extension with antioxidants such as vitamins, superoxide dismutase, catalase and metallothionein [8]. Accumulation of the pro-oxidant **advanced glycation end-products (AGEs)** lays the foundation for the ‘glycation theory of aging’ [3]. Given the critical role of mitochondrial energy supply in organismal homeostasis, the ‘mitochondrial decline theory’ favors a decline in mitochondrial capacity and function (ATP production) in the aging process [2, 3]. In addition to their role in energy supply, mitochondria also function as the main sites for reactive oxygen species (ROS) production courtesy of mitochondrial respiration [3], coinciding with the aforementioned “free radical theory”. Mitochondrial defect in aging may result from loss of mitochondrial integrity following **mitochondrial permeation transition pore (mPTP)** opening [3, 9]. In addition, telomere shortening has been reported to govern cell replication and senescence with defective telomere possibly serving as a marker for cardiac aging [2]. Furthermore, increased adiposity and metabolic derangement cause premature aging and cardiac aging possibly through inflammation and mitochondrial injury [10, 11]. It is thus imperative to identify the mechanisms of action underscoring deteriorated cardiac reserve and function with aging, with an ultimate goal to offer effective measures to halt or manage the course of biological and cardiac aging.

Recent findings has suggested a role for autophagy, a highly conservative process governing the clearance of long-lived or damaged organelles or cellular components, in the regulation of longevity and cardiovascular function in aging [12-15]. While previous reviews had focused on the cell-autonomous nature of autophagy in aging, relevant drug therapies targeting autophagy is less clear in longevity and cardiovascular aging. Through examining

the relationships among autophagy, longevity and cardiovascular aging, this review aims to explain how autophagy dysregulation shapes cardiovascular in particular cardiac aging. We will discuss how these basic concepts can be translated to pharmacological therapy of lifespan and healthspan.

Autophagy and autophagy regulation in lifespan and aging

Autophagy denotes a cellular process for degradation and recycling of long-lived or damaged organelles and proteins, including *microautophagy* - the invagination of lysosomal membranes, *chaperone-mediated autophagy (CMA)* – shipping of soluble proteins to lysosomes through chaperones and lysosomal membrane receptors, and *macroautophagy* (or autophagy) – engulfing cargos via double-membrane autophagosomes prior to fusion with lysosomes [12, 16-18]. Autophagy is initiated by the class III phosphatidylinositol-3 kinase (PI-3K) and Beclin-1. Autophagosomes undergoes elongation, microtubule light chain-3 (LC3) recruitment, proteolytic cleavage of LC3 (lipidation) and formation of autophagolysosomes (autophagosome fusion with lysosomes). Autophagy may be divided into selective and non-selective forms depending on the nature of cargo contents (such as **mitophagy** for selective tagging and degradation of long-lived or injured mitochondrial organelles). Two types of mitophagy are present namely the PTEN-induced putative kinase 1 (Pink1)/Parkin and the mitophagy receptors [BCL2 19 kD Protein-Interacting Protein 3 (BNIP3) and FUN14 domain containing 1 (FundC1)] [11]. As shown in Fig. 1, autophagy process is stimulated by AMP-dependent protein kinase (AMPK) and is suppressed by Akt and mechanistic target of rapamycin (mTOR) [16, 17]. The serine/threonine kinase mTOR is sensitive to changes in amino acids, fatty acids, growth factors such as insulin and insulin-like growth factor 1 (IGF-1), and regulates cell growth and metabolism [19]. Autophagy participates in a wide variety of physiological and pathophysiological processes such as growth and development, metabolism, inflammation, neurodegenerative diseases, cancer, metabolic and cardiovascular diseases. Autophagy may be both adaptive and maladaptive through promoting cell survival or conversely, cell death with excessive autophagy (i.e., **autosis**) [20]. Dysregulated autophagy is evident in cardiovascular aging as well as other forms of cardiovascular pathologies including heart failure, myocardial hypertrophy, ischemic heart disease, hypertension, stroke, diabetes and alcoholic complications [11, 15, 18, 20].

Ample of evidence has suggested a role for autophagy in the survival and longevity through removal and recycling of long-lived or injured cellular components or proteins [18, 20, 21]. Autophagy declines with aging while pharmacological and genetic approaches for lifespan extension are closely related with autophagy induction [8, 12, 16]. Table 1 summarizes the effect of genetically-modified autophagy gene and autophagy regulators on lifespan and cardiovascular aging in rodents. Similar findings were also noted in lower species providing the genetic link of Atg autophagy genes with longevity (reviewed in [21]). In general, suppression of autophagy induces cell death, accelerates aging and shortens lifespan [21]. This is in line with the notion that autophagy failure or mutation in autophagy genes promotes premature aging, cardiac aging and neurodegenerative diseases (including Parkinson disease, spastic paraplegia and ataxia), in association with buildup of damaged intracellular components, disturbed cellular homeostasis [3, 8, 16, 21, 22]. This is supported

by the apparent cardiovascular anomalies in loss-of-function autophagy models [3, 8, 16]. In lower species, muscle and cardiac aging are characterized by progressive accumulation of protein aggregates associated with impaired function in Drosophila. Forkhead Box O transcriptional factor (FOXO) overexpression and increased activity of its target Thor/4E-BP preserve muscle function and extend lifespan via autophagy induction [23, 24]. Atg8b, one autophagy-associated gene, was downregulated with age in Drosophila heart. Age-dependent ectopic fat accumulation (EFA) in non-adipose tissues contributes to metabolic diseases such as obesity in aging. Chaperone dHsc4-assisted autophagy inhibits aging-dependent EFA and extends lifespan in Drosophila by maintaining the proteostasis of lipid droplets [25].

Several explanations can be considered for dysregulated autophagy in aging, among which mTOR serves as the main driving force for autophagy inhibition, aging and lifespan control [8, 19]. A number of lifespan regulatory molecules including **Sirtuins,** AMPK, insulin/IGF-1, and FOXO transcription factors all converge at mTOR [8, 19]. Inhibition of the TOR pathway extends lifespan in yeast, *C. elegans*, Drosophila and rodents [19, 26]. Extension of lifespan with caloric-restriction is mediated through mTOR suppression, supporting the role of mTORC as a bona-fide target for lifespan extension. Activation of mTOR with tuber sclerosis complex 1 (TSC1) conditional deletion in young mice presented aging phenotypes [19]. Intermittent, life-long administration of the mTOR inhibitor rapamycin extends lifespan and suppresses aging-induced weight gain [27]. These findings favor the rationale of targeting mTOR in lifespan control. Given that calorie restriction is not practical in the elderly, due to malnutrition and immunodeficiency, the use of mTOR inhibitors as a ‘gerosuppressants’ to manage senescence and related comorbidities has received much attention [17]. Nonetheless, it may be argued that lifespan extension with mTOR inhibition may be due to alternate mechanism independent of autophagy such as the inhibition of protein synthesis. Deletion of S6K1, the downstream protein synthesis effector of mTOR, effectively prolongs lifespan and retards aging complications. Rapamycin was unable to offer lifespan extension with S6K overexpression [12]. More evidence revealed that mTORC1 phosphorylates the serine/threonine kinase unc-51-like kinase 1 (ULK1 or Atg1), an initiator of autophagy, while rapamycin upregulates Atg1 and promotes autophagy, even with surplus of nutrients [8].

Findings from our lab indicated that activation of the mTOR upstream signal Akt accentuated cardiac aging (both geometry and function) through dampened autophagy (as depicted in Fig. 1). Our data revealed that induction of autophagy rescued aging-induced cardiac anomalies [28]. Evaluation of autophagy regulatory machineries revealed suppressed tumor suppressor phosphatase and tensin homolog deleted from chromosome 10 (PTEN), AMPK and ACC in conjunction with elevated PI-3K/Akt/mTOR signaling. Along the same line, our recent report indicated that obliteration of Akt2 extended lifespan and rescued against cardiac aging through restored Foxo1-mediated autophagy and mitophagy [15]. This is consistent with the earlier notion that PI-3K inhibition stimulated autophagy, suppressed senescence and preserved contractile function in murine hearts [29]. In addition, data from our group also suggested a role for the innate pro-inflammatory mediator toll-like receptor 4 (TLR4) in declined autophagy and cardiac remodeling and contractile dysfunction in aging, via a histone deacetylase (HDAC1)-nuclear receptor corepressor 1 (NCoR1)-dependent

mechanism [13]. These findings support a unique role for dysregulated autophagy in cardiac aging [15, 16].

Intervention of cardiac aging by targeting autophagy

Although caloric restriction appears to be the most robust way for autophagy induction and lifespan extension through improved mitochondrial respiration and retarding aging comorbidities [2], it may not be ideal for the elderly due to immunodeficiency and malnutrition. A number of anti-aging interventions became available to improve healthspan and/or lifespan, and display beneficial effects against cardiac aging [2, 30]. As shown in Fig. 1, several natural compounds may function as caloric-restriction mimetics including rapamycin, and the AMPK/Sirt1 activators resveratrol and metformin as well as polyphenol products to improve the healthspan in aging [2, 31]. Given the essential role of autophagy dysregulation in cardiac aging [8, 16], we will update the contemporary understanding of rapamycin, resveratrol, metformin, nicotinamide and **NAD$^+$ precursors**, and other compounds in the management of aging and cardiac anomalies related to autophagy regulation (Table 2). Non-pharmacological approaches such as caloric restriction and recent epigenetic intervention will also be discussed.

Rapamycin and mTOR inhibitors

Rapamycin is a US Food and Drug Administration (FDA)-approved mTOR inhibitor and autophagy inducer [19]. mTOR presents as mTORC1 and mTORC2 with distinct structures and activities. mTORC1, composed of mTOR, Raptor, mammalian lethal with SEC13 protein 8 (mLST8), proline-rich Akt substrate of 40 kDa (PRAS40), is rapamycin-sensitive and essential for autophagy regulation. mTORC2, on the other hand, consists of Rictor, mSin1, mLST8 and is rapamycin-insensitive [19]. Rapamycin and its analogs (termed rapalogs such as RAD001) are used in clinical settings such as suppression of organ rejection after kidney transplantation, occlusion of cardiac stents, and certain cancers. Inhibition of mTOR extends lifespan in various organisms including *C. elegans*, Drosophila and mice [19, 32]. The National Institute on Aging (NIA) Intervention Testing Program found extension of lifespan after rapamycin treatment beginning at 9 or 18 months of age in mice [26]. Rapamycin benefits cardiac aging and age-related diseases such as Alzheimer's disease [33, 34]. Short-term rapamycin treatment (10 weeks) improves diastolic function and attenuates LV hypertrophy in aged mice [35]. Along the same line, late-life administration of rapamycin reverses aging-related cardiac dysfunction [36]. The beneficial effect of rapamycin on cardiac aging is likely due to proteomic and metabolic remodeling as it promotes mitochondrial content, inhibits inflammation and reverses aging-associated metabolic switch from fatty acid oxidation to glycolysis [7, 36]. Rapamycin is capable of re-inducing proliferation by lifting cell cycle inhibition, therefore allowing transition from "an irreversible arrest into a reversible state" without forcing cells to proliferate in the event of cell cycle arrest [37]. Interestingly, similar findings were noted in young mice following a 3-month rapamycin treatment [38], denoting an age-independent effects for rapamycin. More evidence suggested that rapamycin is capable of altering the balance between nuclear- and mitochondrial-encoded oxidative phosphorylation, with the mito-nuclear imbalance serving as a conserved mechanism for mitochondrial unfolded protein response (UPRmt) and

longevity [39]. Although inhibition of mTOR is beneficial for cardiac aging, complete removal of mTORC1 may lead to cardiomyopathy, impaired hypertrophic response and accelerated heart failure [40]. Adaptive hypertrophic response is common and deemed adaptive in response to pressure overload or hemodynamic stress in aging.

Resveratrol and Sirtuin activators

The class III histone deacetylases, the NAD^+-dependent Sirtuins, are appealed as "the fountain of youth" with a pivotal role in longevity and aging anomalies. Resveratrol, the first natural flavonoid found in red wine, mulberries, peanuts, and rhubarb, exerts cardiovascular and antiaging benefits through Sirtuin activation in a variety of pathological conditions [41, 42]. Resveratrol produces its beneficial effect on cardiac aging via Sirt1/PI3K/Akt-mediated Foxo3 phosphorylation, mitochondrial preservation and inhibition of cAMP phosphodiesterase, resulting in improved cardiac function [43]. Sirt3 deficiency abrogated the protective effect of resveratrol against cardiac hypertrophy [44]. Furthermore, administration of Longevinex, a commercialized resveratrol formulation, improves cardiac performance and longevity through induction of autophagy, upregulation of Sirt1 and Sirt3 and nuclear translocation of FOXOs in the heart [45]. More evidence has suggested that resveratrol and Sirtuins confer longevity and cardiac benefits through protein hypoacetylation in autophagy control [45]. It is noteworthy that resveratrol inhibits the Akt-insulin signaling promoting Class I PI3K by competing with ATP for the catalytic site, which may promote longevity independent of Sirtuins [46].

Metformin, Berberine and AMPK activators

Metformin is an anti-diabetic drug capable of stimulating AMPK via direct phosphorylation of Ser^{633} and Ser^{1177} [47]. Metformin extends lifespan and improves healthspan in *C. elegans* and mice via mitohormetic regulation of ROS production, AMPK-mediated induction of autophagy and elevation of NAD^+ levels [47, 48]. Data from our lab suggested that short-term treatment of metformin improved cardiac aging phenotype in mice [49]. Findings from the United Kingdom Prospective Diabetes Study revealed that metformin lowers the 10-year mortality in myocardial infarction, stroke, or all-causes compared with sulfonylurea, insulin, or dietary control [50, 51]. The natural occurring compound Berberine lowers serum LDL cholesterol and benefits healthspan through AMPK activation [52]. Berberine enhances autophagy through inhibition of mTOR to limit cardiac remodeling, collagen deposition, apoptosis and fibrosis, resulting in improved cardiac function [53]. In patients with chronic congestive heart failure, berberine improves cardiac function and decreases mortality of the patients during long-term follow-up [54]. More evidence revealed that Berberine retards H_2O_2-induced senescence, in association with restored autophagic flux and NAD^+ levels in senescent cells [55]. Berberine also alleviates postoperative cognitive defects via suppression of neuroinflammation in aging [56]. In addition to AMPK and autophagy induction, other signaling machineries have also been implicated in berberine-elicited anti-aging benefits such as Sirt1, PGC-1α and ATP production [57].

Nicotinamide and NAD^+ precursors

NAD^+ levels decrease with aging due to age-related CD38 upregulation or downregulation of nicotinamide phosphoribosyl transferase (Nampt), a key enzyme for NAD^+ synthesis

[16]. NAD^+ depletion is found in neurodegenerative diseases, and cardiovascular aging, which could be rescued by pharmacological intervention to bolster cellular NAD^+ levels [58]. Chronic intake of the NAD^+ precursor nicotinamide or the specific CD38 inhibitor 78c improves healthspan but not lifespan. Nicotinamide may accelerate autophagy degradation of mitochondria (mitophagy) and improve glucose homeostasis in association with less hepatic steatosis and inflammation, increased glycogen deposition and clearance through glycolytic pathways [59]. Sadoshima and colleagues indicated that NAD^+ precursors including nicotinamide mononucleotide and nicotinamide riboside or upregulation of Nampt may suppress cardiac aging through activation of Sirtuins, including Sirt1 and Sirt3, en route to protein deacetylation and activation of autophagy [16]. Targeted NAD metabolome analysis revealed decreased levels of nicotinamide mononucleotide salvage in nicotinamide mononucleotide-treated mice, an effect offset by overexpression of de novo NAD biosynthetic enzymes. Although nicotinamide mononucleotide may not drastically enhance NAD^+ levels, it may promote acetylation of Sirtuin targets and alleviate cardiac aging in the absence of survival effects [59].

Spermidine

Spermidine is a polyamine participating in an array of biological events including autophagy induction, DNA stability, transcription, translation and apoptosis. Supplementation of spermidine, an autophagy-inducing agent, protects against neurodegeneration and cognitive decline, memory loss and motor impairment in aging. Eisenberg and colleagues recently reported that spermidine improved lifespan and health span through autophagy activation [60]. Using proteomics and metabolomics analyses, these investigators identified proteins and metabolites up- or down- regulated by spermidine in aging rat hearts. The molecules identified were mainly associated with immunity, blood coagulation, lipid metabolism, and glutathione metabolism [61]. To this end, spermidine may offer protective effect against aging hearts and display therapeutic promises in cardiac aging. Further study confirmed that supplementation of spermidine-rich plant extract is safe and well-tolerated in the elderly and mice, making it practical for longer-term intervention of spermidine in humans [62]. At this point, dietary polyamine (spermidine in particular)-offered cardiovascular endpoints seems to be attributed to mitochondrial homeostasis, anti-inflammation, and delay of stem cell senescence [63].

Osteopontin (OPN) Inhibitor

Biological aging is often tied with increased adiposity [11, 17] although the precise interplay remains elusive. Recent work from Derumeaux and colleagues suggested that visceral adipose tissue (VAT) triggers OPN expression and drives interstitial fibrosis in aging hearts. Given that cardiac aging is commonly associated with elevated adiposity and extracellular matrix including OPN (a marker for cardiac anomalies including calcification), these investigators tested the effect of surgical removal of VAT and a small-molecule OPN inhibitor Agelastatin A on cardiac aging. Interestingly, VAT removal significantly reduced circulating levels of OPN and TGFβ, restored cardiac function and alleviated myocardial fibrosis in aging hearts, the effects of which were mirrored by OPN deficiency. VAT removal and OPN deficiency promoted senescence of cardiac fibroblasts and thus limited their activation. Agelastatin A reversed aging-related cardiac fibrosis and dysfunction [10]. These

findings supported the nature of VAT as the main source of OPN in aging to compromise cardiac structure and function through profibrotic secretome. Although a role for autophagy has not yet been identified here, OPN is well known to promote autophagy [64] thus raising a possible beneficial effect of autophagy inhibition in aging. Interventions targeting OPN such as VAT removal and OPN inhibition may be promising therapeutic targets for cardiac aging possibly through induced fibroblast senescence [10].

Fibroblast growth factor 21 (FGF21)

FGF21 belongs to a hormone-like FGF family and serves as a longevity factor governing energy expenditure, stress responses, glucose and lipid metabolism. In ER stress, dysfunctional mitochondria and autophagy, FGF21 regulates stress and metabolism through somatotropic and hypothalamic-pituitary-adrenal (HPA) axis. It was demonstrated that FGF21 alleviates aging pathologies in metabolism such as type 2 diabetes, obesity, atherosclerosis and cardiovascular diseases. Overexpressing FGF21 prolonged lifespan in mice although FGF21 resistance may develop under metabolic and stress-related disorders to compromise healthy aging [65]. Several mechanisms have been postulated for FGF21-induced healthy aging in integrated stress response including AMPK activation, autophagy induction and anti-inflammation. Likewise, FGF21 resistance, may jeopardize human healthspan and accelerate the aging process through disturbed autophagy, similar to insulin resistance [65].

Urolithin A and mitophagy regulators

Aging is commonly associated with mitochondrial dysfunction and compromised mitophagy [66]. However, effective measures to enhance mitochondrial function in particular mitophagy are still lacking due to toxicity and non-specificity. Urolithin A, a natural compound that induces mitophagy, was found to extend lifespan and promote health aging likely through mitophagy and clearance of injured mitochondria. Rye and colleagues revealed that urolithin A improved various activity (e.g., mobility, pharyngeal pumping and exercise capacity) and maintained mitochondrial respiration in aging in *C. elegans* and rodents [67]. Urolithin A and other food consumption components including asnicotinamide riboside and tomatidine, may protect against age-related loss in muscle function (sarcopenia) [67]. These findings highlight the health benefits of urolithin A and mitophagy enhancers in preservation of mitochondrial and cardiac function in aging.

Other anti-aging drugs with autophagy regulatory potential

There are a number of additional anti-aging drugs with promises in autophagy regulation. As shown in Table 2, N-acetyl-glucosamine and b-Guanidinopropionic acid may prolong lifespan through facilitated autophagy [68, 69]. In addition, natural compounds curcumin and melatonin have also exhibited beneficial responses against cardiovascular aging [70, 71] although direct evidence is still lacking for a permissive role of autophagy herein. Kallistatin is an endogenous protein although recent evidence suggested some promises for Kallistatin in lifespan extension and protection against senescence through inhibition of Akt-Bcl2, upregulation of Sirt1 and inhibition of oxidative stress and inflammation [72, 73].

Caloric restriction and lifestyle modification

In addition to pharmacological interventions, lifestyle modification such as caloric restriction also slows aging, extends lifespan and counters age-related diseases in various species [17, 74]. Epidemiological, clinical and experimental studies have all confirmed the benefits of caloric restriction in extended lifespan and healthspan, and benefited cardiac aging through autophagy induction [74]. Suppression of mTOR and induced autophagy were noted in calorically restricted hearts, indicating contribution of mTOR-dependent autophagy in caloric restriction-elicited benefit in cardiac aging [75]. Moreover, autophagy improves neuroendocrine and metabolic profiles of adiposity, glucose and lipid metabolism in aging [16, 17]. Pharmacological autophagy induction reduces serum leptin levels whereas genetic removal of leptin triggers autophagy. Decreased autophagy in aging may also be attributed to lipid accumulation and metabolic derangement with age [76]. Autophagy controls the formation of lipid droplets in the heart, with autophagy failure prompting accumulation of triglycerides and lipid droplets [76].

Epigenetic intervention

Aging is associated with altered epigenetic profiles of both DNA and histones such as DNA methylation and histone acetylation and methylation, while longevity intervention may attenuate age-associated chromatin decline [77]. Several epigenetic-targeting drugs have received FDA approval and many others are under clinical trials (although most for cancer therapy). A number of bioactive phytochemicals such as metformin and caloric restriction have been shown to possess epigenetic modulatory activities in aging (Table 2) [77]. These epigenetic modulators delay aging and minimize the risk of cancer. For example, chromatin alterations are indicated in the pathophysiology of age-related disease. The “designated epigenetic modulators” in cardiac aging are still unknown and little information is available for the role of autophagy regulation herein. It is thus intriguing to find out how much overlap exists between the current list of cardiovascular aging interventions and the epigenetic phenotypes these drugs may influence.

Conclusion and future perspectives

Evidence has suggested that autophagy is essential to longevity and healthspan, and altered autophagy contributes to cardiac aging and the transition of healthy state of organism into a pre-senescent state [12, 21, 78]. Although autophagy inducers have been indicated to benefit lifespan and aging cardiovascular pathologies [12], controversy still exists in term of the protective versus deleterious effect of autophagy induction in aging complications [79] (see Outstanding Questions). Much challenges remain for the field of aging. Multiple organismal models are used to dissect the correlation between aging and autophagy, although it is unclear with regards to the model specificity for autophagy in aging. Although autophagy is permissive to longevity, it remains unclear whether cardiac aging develops as a consequence of autophagy decline in aging or vice versa. Besides the therapeutic options discussed here in this review, more viable anti-aging regimen are available based on the activation of telomerase, NO modulation, antioxidants, PARP inhibition, senolytic therapeutics, plasma membrane redox system (PMRS) activators, and stem cell therapies [2]. Involvement of

autophagy regulation is less clear for these measures. In-depth understanding of the mechanism behind autophagy dysregulation in aging and aging-related cardiovascular anomalies is vital for the development of appropriate therapeutic strategies to halt aging and cardiac complications in aging.

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Glossary:

Autosis:
a form of cell death triggered by autophagy mediated by Na^+-K^+-ATPase pump.

Advanced glycation end-products (AGEs):
a subset of glycated and oxidized proteins and lipids after continued contact of reducing sugars or short-chain aldehydes with amino group.

Cardiac reserve:
the ability of heart to expel a larger quantity of blood beyond the basal level.

Diastole:
relaxation and dilation of the heart chambers.

Mitophagy:
the specific autophagic elimination of mitochondria.

Mitochondrial permeation transition pore (mPTP):
protein formed in the inner membrane of the mitochondria under pathological conditions, the opening of which leads to cell death.

NAD precursors:
molecules with NAD producing ability, including nicotinamide and vitamin B3 derivatives such as nicotinamide riboside and nicotinamide mononucleotide.

Selective autophagy:
autophagy process involving recognition and targeting of specific cargo, such as damaged organelles, misfolded proteins, or invading pathogens for lysosomal destruction.

Sirtuins:
NAD-dependent deacetylases governing metabolism, healthspan, and aging.

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Outstanding Questions:

- Given the heavy use of multiple organismal model in aging and autophagy field, do changes in autophagy vary across model/species in aging?
- Do changes in autophagy exhibit organ and tissue specificity, even in the same organism?
- Besides mTOR, what else could contribute to aging-associated decline in autophagy?
- Do pharmacological activation and inhibition of autophagy both offer benefits against aging?
- Are autophagy different in aging based on the form of autophagy (selective or non-selective) ?
- Are changes in autophagy results of metabolic derangement in aging or vice versa (failure to clear excess lipids in aging)?

Highlights

- Clinical and experimental data depicted a tie between age-related cardiovascular diseases and autophagy failure.
- Autophagy deficiency shortens lifespan and compromises cardiovascular function in aging.
- Autophagy induction delays aging, prolongs lifespan and, improves cardiac aging.

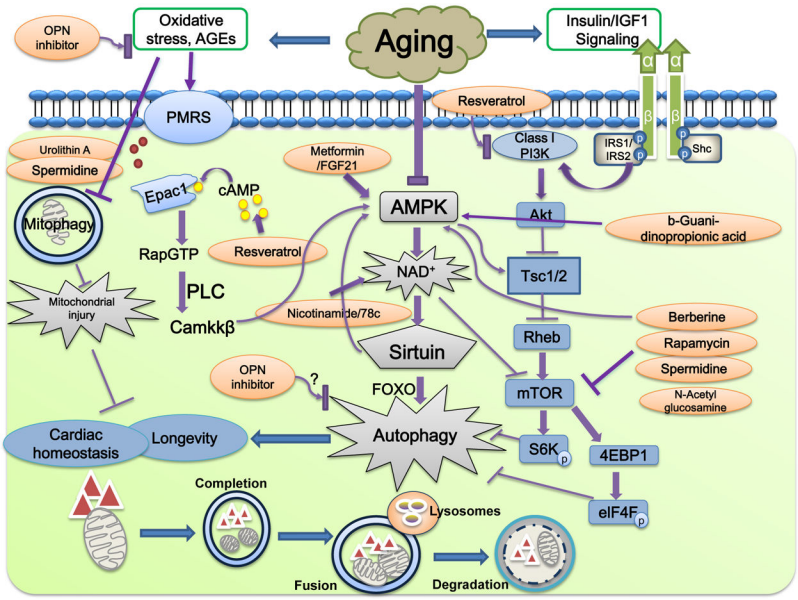

Fig. 1:

Schematic diagram depicting dysregulation of autophagy in advanced aging and how various pharmacological interventions may intervene the autophagy signaling process. Aging is commonly associated with impaired autophagy and mitophagy. Two main regulatory signaling machineries involved in dysregulated autophagy are suppressed AMPK activation and elevated class I PI-3K/Akt signaling, resulting in overactivated mTOR signaling, autophagy failure and changes in longevity and cardiac homeostasis. Improved lifespan and cardiac function in aging may be achieved through activation of AMPK directly or NAD^+-dependent sirtuins indirectly. Sirtuins in turn promote longevity through FOXO-dependent induction of stress response and autophagy. Some pharmacological anti-agents such as resveratrol may benefit longevity and cardiac aging through autophagy-independent mechanism such as cAMP accumulation, leading to phospholipase C (PLC)-mediated activation of CamKKβ. Rapamycin, spermidine and N-acetyl glucosamine are considered autophagy inducers to directly act on mTOR. Free radical accumulation and oxidative stress such as AGEs turn on multiple oxido-reductase enzymes in aging commonly known as plasma membrane redox system (PMRS) that regulates cellular redox homeostasis and mitochondrial integrity. Bottom panel displays the essential steps in autophagy including nucleation and elongation, completion, fusion between autophagosomes and lysosomes as well as lysosomal degradation. Abbreviations PMRS: plasma membrane redox system, IGF-1: insulin like growth factor-1, FOXO: Forkhead O transcriptional factor; IRS: Insulin receptor substrate; EPac1: exchange protein directly activated by cAMP; OPN: osteopontin; CamKKβ: Ca^{2+}/calmodulin-dependent protein kinase kinase β; mTOR: mammalian target of Rapamycin, PI3K: Phosphatidylinositol 3-kinase.

Table 1:

Lifespan and cardiac aging in genetically engineered murine models of autophagy

Genotype	Target organ	model	Lifespan and cardiovascular aging	Reference
Atg5−/− neonatal mice	Global	starvation	Normal at birth but die within 1 day of delivery, survival time of starved Atg5-deficient neonates (12 h) < wild-type mice (21 h)	[80]
Atg5 transgenic mice	Global	aging	anti-aging phenotypes, including leanness, increased insulin sensitivity and improved motor function	[81]
Transgenic HSP27 mice	Cardiac specific	aging	Attenuates aging-induced impairment of cardiac function	[82]
$Akt1^{+/-}$mice	Global	aging	Reduced ribosomal biogenesis, mitochondrial DNA content and oxidative stress	[83]
Akt2 −/− mice	Global	aging	prolongs life span and improves myocardial contractile function with adaptive cardiac remodeling	[15]
hypomorphic (mTOR(Δ/Δ)) alleles mice	Global	aging	increases lifespan, exhibits a marked functional preservation in various organs	[84]
heterozygous mice lacking global/hepatic Rictor, global Rictor deletion mice	Liver, global	aging	decreases male, but not female, lifespan, independent of the role of hepatic mTORC2 in promoting glucose tolerance	[85]
S6K1−/−mice	Global	aging and high fat diet	protects against obesity due to enhanced beta-oxidation, sensitive to insulin owing to loss of a negative feedback loop from S6K1 to insulin receptor substrate 1 (IRS1), which blunts S307 and S636/S639 phosphorylation	[86]
a Phe121Ala mutation in beclin 1 ($Becn1^{F121A/F121A}$) to interrupt interaction with BCL2	Global	aging	Increases lifespan, diminishes age-related renal and cardiac pathological changes and spontaneous tumorigenesis via Disruption of the beclin 1-BCL2 autophagy regulatory complex	[14]
TSC1 transgenic mice	Global	aging	lifespan extension in female, but not male	[87]

Table 2:

List of anti-aging drugs with cardiovascular benefits involving autophagy induction

Drug	Species	Lifespan & cardiovascular response	Possible mechanisms	Reference
Rapamycin	Rodents, human (Hutchinson-Gilford progeria syndrome)	Prolongs lifespan, reverses age-related oxidative stress, cardiac and vascular dysfunction, reverses cellular phenotype of fibroblasts from children	Activates AMPK, inhibits mTOR, S6 kinase and ULK1 phosphorylation, induces autophagy, clears progerin through autophagy, promotes mitochondrial biogenesis.	[26, 88-90]
Resveratrol	Rodents, human, Yeast, C. elegans, Drosophila	Prolongs lifespan, improves cardiac and vascular function as well as mitochondrial number but not glucose metabolism in aging	Activates AMPK and Sirtuins, mimics calorie restriction, affects acetylproteome, promotes lipolysis and attenuates lipogenesis	[91-93]
Metformin	Rodents, human aortic endothelial cells, C. elegans, Drosophila	Prolongs lifespan, improves Physiological and metabolic parameters in aging (glucose tolerance, exercise capacity and cardiac function), delays endothelial senescence via mitochondrial biogenesis/function	Activation of AMPK, H3K79 methylation, inhibits mTOR, reduces hyperglycemia and hyperinsulinemia and alleviates insulin resistance	[94, 95]
Nicotinamide derivatives, specific CD38 inhibitor 78c	Rodents, human	Improves healthspan but not lifespan, reverses age-related NAD^+ decline and improves cardiac function in natural and accelerate aging	Stimulates autophagy and mitophagy, increases NAD+ levels, activation of Sirtuins, AMPK and poly (ADP ribose) polymerases (PARPs)	[59, 96]
Spermidine	Rodents, human, yeast nematodes and flies	Prolongs lifespan, improves healthspan, reduces cardiac hypertrophy and remodeling, preserves diastolic function in aging, reduces blood pressure and incidence of cardiovascular disease and cancer mortality	Induces autophagy, Mitophagy and mitochondrial respiration, inhibits histone acetyltransferases, inflammation, oxidative stress, affects glutathione metabolism, lipid metabolism	[60, 61, 63, 93]
OPN inhibitor Agelastatin A	Rodents	Rescues cardiac aging and induces a selective fibroblast senescence	Modulates fibroblast senescence by osteopontin (OPN) production.	[10]
Fibroblast growth factor 21 (FGF21)	Rodents, C. elegans	Improves healthspan and extends lifespan; alleviates age-related metabolic disorders, including atherosclerosis, obesity, type 2 diabetes	Activates AMPK, Autophagy and anti-inflammation	[65]
Urolithin A	Rodents and C. elegans	Prolongs lifespan, improves healthspan, exercise capacity and	Stimulates mitophagy, prevents accumulation of dysfunctional mitochondria	[67]

Drug	Species	Lifespan & cardiovascular response	Possible mechanisms	Reference
		mitochondrial function		
N-Acetyl-glucosamine	C. elegans	Extends mean lifespan	Enhances autophagy, ER-Associated protein degradation, and proteasomal activity	[68]
Curcumin	Human	Improves vascular endothelial function in healthy middle-aged and older adults.	Increased nitric oxide (NO) bioavailability and reduced oxidative stress	[71]
b-Guani-dinopropionic acid	Drosophila melanogaster	Prolongs lifespan	Activates autophagy by AMPK-Atg1 signaling pathway	[69]
Kallistatin	Rodents, C. elegans	Extends lifespan, reduces vascular senescence and aging.	MicroRNA-34a-Sirt1-dependent	[72, 73]
Melatonin	Cardiac progenitor cells	Antagonizes premature senescence of cardiac progenitor cells	H19/miR-675/USP10-depndent pathway	[70]