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Metabolic Stress, Autophagy and Cardiovascular Aging: from Pathophysiology to Therapeutics

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Abstract

Recent advances in health care have improved the management for cardiometabolic disorders, and prolonged life span. However, the ever-rising prevalence of metabolic stress related to the pandemic obesity epidemic (insulin resistance, diabetes, hypertension, dyslipidemia) has greatly challenged geriatric care. The ubiquitin-proteasome system and autophagy-lysosomal pathways represent two major, yet distinct cellular machineries, for degradation and removal of damaged or long-lived proteins and organelles, the function of which declines with aging. To seek new strategies for cardiovascular aging under various metabolic diseases, it is imperative to understand the precise role for metabolic stress and protein quality control in particularly autophagy in premature cardiovascular aging process. Targeting metabolic stress and autophagy may offer exciting new avenues for the management of cardiovascular aging.

Keywords

Metabolic stress; obesity; aging; cardiac; autophagy

CARDIOVASCULAR AGING AND PATHOPHYSIOLOGY

The human life expectancy rose dramatically over the past decades, leading to a fast-growing aging population. The elderly population (> 65 years of age) is estimated to jump from 10% of the population in 2000 to ~ 22% by 2050 and an alarming 32% in 2100 [1]. Measures to achieve healthy aging and alleviate aging-related morbidities become a burning issue for health care. One major threat with the ever-rising aging population is the

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prevalence of aging-associated cardiovascular morbidity and mortality such as atherosclerotic vascular dysfunction [2]. Ample of clinical evidence has suggested much higher mortality of myocardial infarction or stroke in patients with progeria (premature aging) syndrome [3]. Cardiovascular diseases such as arterial hypertension, and heart failure impose a huge economic burden to the society [2, 3], warranting a better knowledge of molecular mechanisms behind declined cardiovascular function in the elderly and adults with premature aging. This supports not only the main objective for geriatric clinical care to effectively manage or halt the progression of cardiovascular aging, but also the therapeutic rationale for adult patients with metabolic diseases. In addition, the prevalence of aging-related health issues accelerate in lower income communities with less access to health care, suggesting an economic impact on healthy aging [4].

The normal aging process presents progressive deterioration in organ structure and function, such as in cardiovascular aging (Text Box 1), which is influenced by genetic and environmental factors. Several theories were postulated for cardiovascular aging, such as oxidative stress, DNA damage, telomere shortening, apoptosis and dampened autonomic response. In addition to these pathophysiological changes, other factors may also contribute to cardiovascular aging including neurodegeneration and metabolic derangements (obesity, diabetes mellitus, dyslipidemia, low- grade inflammation, insulin resistance and hypertension) [3, 5, 6]. However, insufficient evidence is available to validate these theories in the clinical settings. Moreover, while aging is the independent risk factor for these metabolic disorders [3, 6], limited evidence is seen for the link between these metabolic derangements and premature aging. Here we will summarize recent clinical, epidemiological and experimental findings on how metabolic anomalies (such as obesity, diabetes mellitus, dyslipidemia, insulin resistance and hypertension) may foster premature cardiovascular aging, and give insights into the cellular aspects of metabolic stress and dysregulated autophagy, as well as potential therapeutic strategies for the management of premature cardiovascular aging.

IMPACT OF METABOLIC STRESS ON CARDIOVASCULAR HEALTH

a. Metabolic disease - brief overview and the cardiovascular sequelae

The prevalence of metabolic diseases including obesity, diabetes mellitus, insulin resistance, dyslipidemia and hypertension has reached an exponential rise recently, largely due to lifestyle factors such as high fat/caloric intake, smoking and satiety [6–9]. The metabolic comorbidities often cluster together, known as metabolic syndrome [10]. Metabolic syndrome is defined by the National Institutes of Health (NIH) by meeting at least three of the following conditions: obesity, elevated triglycerides, low high-density lipoprotein cholesterol (HDL-c), hypertension or elevated fasting plasma glucose [11]. Among these factors, obesity imposes the most severe health outcome (Fig. 1). Even a modest rise in body weight may place a considerable burden on type 2 diabetes risk and health care, through dyslipidemia including elevated levels of triglycerides, apolipoprotein B, low-density lipoprotein cholesterol (LDL-c), low HDL-c, low- grade inflammation, and endothelial injury [8, 11, 12]. Metabolic disorders are associated with unfavorable changes in cardiovascular geometry and function including cardiac and vascular remodeling, neointimal

formation, decreased myocardial contractility, endothelial injury and compromised vascular compliance (Text Box 1) [11, 13, 14]. It is well perceived that individual components of metabolic syndrome serve as independent risk factors for the overall prevalence of cardiovascular disease, with the prevalence drastically escalating with concurrent risk factors [11, 15]. Obesity especially visceral fat distribution is considered the central frame for metabolic disorders prompting the onset and development of insulin resistance, diabetes, hypertension, dyslipidemia, and dementia [8, 14, 16, 17]. Despite some intensive clinical managements to improve cardiovascular outcomes, patients with metabolic syndrome still face suboptimal risk factor management and suffer from premature aging (progeria) or reduced life expectancy [6,–11].

b. Influence of metabolic stress on cardiovascular health in aging

Metabolic diseases and aging are independent risk factors for cardiovascular morbidity and mortality [2–4, 8, 11, 18, 19]. Aging is a major determinant for the high prevalence of metabolic syndrome since the elderly are more prone to the constellation of cardiovascular and metabolic risk factors that constitute the syndrome [3, 9, 20]. Recent evidence also depicted a role for metabolic stress including obesity, insulin resistance, dyslipidemia, diabetes mellitus and hypertension in the premature aging process possibly due to disturbed mitochondrial homeostasis and protein quality control, in particular autophagy [6, 9, 21, 22]. Using the data from cohorts of the National Health and Nutrition Examination Survey (NHANES III, 1988–1994; NHANES continuous, 1999–2010), the increase in maximum body mass index (BMI) over 1988–2011 was estimated to reduce life expectancy at age of 40 by 0.9 years and accounted for 186,000 excess deaths in 2011 [23]. In Australian patients on medication for schizophrenia, meeting the criteria for at least one component of metabolic syndrome is closely linked to the risk of premature death [24]. The association between obesity and reduced life span or years of life lost (YLL) has also been confirmed by other epidemiological studies [4, 19, 25]. Interestingly, the association between obesity and reduced longevity or YLL is much lower in older Caucasian men and in women across all ages [19], suggesting the impact of obesity on premature aging may be more prevalence in adults. A number of pathophysiological factors may be considered for the association between metabolic syndrome and longevity including gender, behavior, causality versus correlation, and experimental models (primates versus mice) [13]. Metabolic diseases are closely related with risk of premature cardiovascular aging (cardiac remodeling, decreased cardiac pump function, vascular remodeling and stiffness, endothelial injury, inflammation and calcification) and elevated risks for heart failure [13, 25]. Here we will dissect how each individual metabolic anomaly may predispose premature cardiovascular aging.

c. Pathophysiology of premature cardiovascular aging

Metabolic diseases contribute to the premature aging process likely through the alteration of metabolic homeostasis [26]. In an era of nutrition excess unprecedented in the human evolution, balanced diet and nutrition helps to maintain an expected life span of 80+ years in industrialized nations [27]. However, various metabolic derangements (obesity, ectopic fat accumulation, Mg^{2+} metabolism alterations, insulin resistance, inflammation, shortening of telomere length, and circadian rhythm disturbances) compromise the normal aging process (such as loss of muscle mass and strength) [28]. A number of theories have been articulated

for the premature aging in metabolic diseases, with many of which recapitulating the classical theories of aging [6, 29]. Among which, the ‘free radical theory of aging’ attributes biomolecules exposure to free radical species, which is supported by extended lifespan from antioxidants such as superoxide dismutase, catalase and metallothionein [29]. Next, advanced glycation end-products (AGEs) build up in aging and dictate the ‘glycation theory of aging’ [6, 29]. In particular, AGEs abridge the “free radical” with the “glycation” theories in aging. The ‘mitochondrial decline theory’ highlights declines in mitochondrial ATP supply manifested as loss of mitochondria and appearance of swollen and defective mitochondria in aging [30]. Telomere shortening governs senescence with defective telomere serving as an indicator of cardiovascular aging [31, 32]. In addition to genetic modulation, epigenetic modifications (such as DNA methylation, histone modification and microRNA) also participate in cardiovascular aging [6, 29]. Finally, protein quality control by way of the ubiquitin-proteasome system (UPS) which ‘flags’ misfolded proteins with ubiquitin for proteolytic degradation, and autophagy which removes cellular aggregates, are dysregulated in aging and contribute to the proteostatic controls in aging [33–35]. Defective protein quality control is associated with proteotoxicity in aging, neurodegenerative disease, type 2 diabetes and cancer [35–37]. Metabolic syndrome in particularly obesity may compromise longevity such as loss of telomere length and downregulation of longevity genes such as sirtuin 1 [38]. Despite an enriched knowledge of the cardiovascular complications associated with biological aging processes [2], the impact of metabolic stress/disease-prompted “acceleration” of cardiovascular aging still cannot be explained simply by a unifying theory.

AUTOPHAGY IN CARDIOVASCULAR AGING - ACTION OF METABOLIC STRESS

a. Biochemistry, regulation and functionality of autophagy

Autophagy, a process for degradation of long-lived or injured organelles and proteins, are present in three forms - *microautophagy*, invagination of lysosomal membranes; *chaperone-mediated autophagy (CMA)*, delivery of cargo macromolecules to lysosomes via chaperones and receptors on the lysosomal membrane; and *macroautophagy*, (autophagy), denoting formation of the double membrane autophagosomes from endoplasmic reticulum, mitochondria or other cellular components prior to their fusion with lysosomes to form autophagolysosomes [8, 35, 39]. The class III phosphatidylinositol-3 kinase (PI-3K) and beclin-1 are responsible for initiation of autophagosomes before elongation governed by autophagy related genes (Atg). The Atg genes recruit microtubule light chain-3 (LC3), and proteolytic cleavage of LC3 to form LC3-II. The outer autophagosome membrane then fuses with lysosomes to form autophagolysosome where cytosolic components are destroyed and removed [8, 35, 39]. Autophagy is activated by AMP- dependent protein kinase (AMPK) while, Akt and mammalian target of rapamycin (mTOR) inhibit autophagy [39, 40]. Autophagy is triggered by caloric and nutrient deprivation as well as certain pathological conditions to preserve cellular homeostasis by ridding off protein and cellular aggregates. However, too much autophagy may be detrimental by extensive cell death - a process termed as “autosis” [8].

b. Autophagy in longevity and cardiovascular homeostasis

Autophagy participates in the maintenance and regulation of cardiovascular homeostasis and pathologies including cardiac hypertrophy, heart failure, cardiomyopathy, coronary heart disease, hypertension and atherosclerosis [8, 39]. Impaired autophagic clearance of protein aggregates exerts unfavorable consequences including mitochondrial injury, compromised cardiovascular contraction, reduced tolerance to ischemic stress, and increased inflammation [41]. For example, cardiac knockout of Atg5, a gene controlling autophagosome formation, resulted in cardiac hypertrophy, LV dilation, contractile dysfunction, and heart failure [42]. Autophagy declines with aging [35]. Inhibition of autophagy accelerates premature aging and shortens lifespan [35] whereas induction of autophagy (via rapamycin, spermidine, metformin or Atg5 overexpression) prolongs lifespan in yeast, flies, worms and mice [43, 44]. Autophagy induction using caloric restriction also increases telomerase activity [45]. Insufficient autophagy or autophagy failure contributes to buildup of intracellular aggregates, leading to disturbed cellular/tissue homeostasis and functional loss in aging [35]. Not surprisingly, pharmacological and genetic interventions favoring longevity are tied to autophagy induction [35, 43, 44]. Recent work from Levine and colleagues observed alleviated premature aging, and promoted longevity in mammals with disruption of the Beclin1-Bcl-2 autophagy complex (which inhibits autophagy) [46]. How autophagy precisely regulates the aging process, longevity and associated cardiovascular homeostasis still remains elusive. One essential signal regulating autophagy in longevity and aging is the serine threonine kinase mTOR presented in two complexes as mTORC1 and mTORC2 [35, 40]. mTORC1 is a rapamycin-sensitive complex of mTOR with Raptor, mLST8, PRAS40 whereas mTORC2 is rapamycin-insensitive consisting of Rictor, mSin1, and mLST8. mTOR is highly sensitive to changes in nutrient environment such as amino acids, fatty acids, growth factors such as insulin and insulin-like growth factor I (IGF-1), making metabolic or nutrient stress a viable regulator of autophagy [40]. Close association exists between mTOR and aging as elevated mTOR activity is found in aged hematopoietic stem cells. Activation of mTOR displayed overt aging phenotypes (decreased lymphopoiesis, impaired hematopoietic cell reconstitution) in young hematopoietic stem cells [47]. Inhibition of mTOR pathway is shown to extend lifespan in multiple species including yeast [48], *C. elegans*, [49] and *Drosophila* [50], and mice [51]. Intermittent (2 weeks/month) chronic intake of rapamycin prolongs life span and counters age-associated weight gain [52]. Inhibition of mTOR alleviated suppressed proliferative potential triggered by ectopic p21 or p16, and transformed arrested cell cycle from “the irreversible arrest into a reversible condition” [35]. Caloric-restriction mediated life span extension is also mediated via downregulation of mTOR [40]. In addition, many genes controlling life span including FOXO transcription factors, insulin, IGF-1, and sirtuins all converge at mTOR [40], making it an attractive target for longevity control. These studies support the notion of mTOR as a bona-fide pharmacological target for lifespan extension, validating the potential of targeting mTOR in cardiovascular aging.

Several lines of evidence have implicated an essential role for compromised autophagy in cardiovascular aging [33]. As suggested in Fig. 2, aging-related cardiovascular anomalies along with mitochondrial defects involve impaired clearance of damaged organelles by autophagy and insufficient replenishment of mitochondrial pool from mitochondrial

dynamics and biogenesis [33, 39, 53]. Autophagy and autophagic flux are suppressed in the aging cardiovascular system. Results from our lab suggested that cardiac-specific activation of Akt, the upstream signal of mTOR, worsened geometric and functional changes in cardiac aging via deteriorated autophagy. Assessment of autophagy regulatory signal revealed enhanced phosphorylation of Akt and mTOR while inhibiting that of PTEN, AMPK and ACC. Rapamycin rescued aging-induced cardiac dysfunction [54]. Further study from our lab revealed that Akt2 ablation extended life span and countered against cardiac aging through restored Foxo1-related autophagy and mitophagy (Text Box 2) [55]. Evidence from epidemiological studies suggested reduced risk for cardiovascular and cancer-related mortality with dietary polyamine uptake (the autophagy/mitophagy inducer spermidine in particular), the benefit of which is likely mediated through preserved mitochondrial function, anti-inflammatory properties, and retardation of stem cell senescence [56]. Loss-of-function autophagy models present poor cardiovascular function accompanied by the accumulation of misfolded proteins and defective organelles. On the other side of the coin, autophagy induction improves cardiovascular function in aging models by removing misfolded proteins, defective mitochondria, and damaged DNA, thus improving the cellular environment and alleviating cardiovascular pathology in aging [33, 55]. These findings favored the notion that loss of autophagy promotes aging-induced cardiovascular anomalies

a. Autophagy in obesity and adiposity-associated cardiovascular aging

Ample of evidence has indicated an association among obesity, overeating and sedentarism, and reduced life span or YLL [4, 19]. Obesity leads to a cascade of pathological changes in the cardiovascular system as depicted in Fig. 1 possibly due to aberrant substrate utilization (higher fatty acid uptake and poor glucose utilization), mitochondrial injury, buildup of lipotoxicity, altered insulin action, and intracellular Ca^{2+} handling to compromise cardiovascular function [8]. In a prospective cohort study from Sweden, increase in BMI was found to be tightly associated with heart failure with valvular disease, coronary heart disease, diabetes or hypertension, revealing a progressively increased risk of heart failure discernible at normal body weights with a ~10-fold jump for severe obesity [57]. These cardiovascular anomalies in obesity promote deterioration of cardiovascular function and onset of premature cardiovascular aging. Niemann and colleagues examined atrial cardiomyocytes from a large cohort of subjects with preserved LV function following coronary artery bypass grafting. They found that young obese subjects exhibited mitochondrial injury, oxidative damage, and apoptosis, reminiscent of older subjects with or without obesity. Further study using Zucker obese rats identified altered levels of genes encoding mitochondrial proteins [25]. Similar findings from our lab also suggested premature cardiac aging and mitochondrial dysfunction in mid-age ob/ob obese mice [58]. More recent finding from Derumeaux's laboratory revealed that visceral adipose tissue triggers osteopontin expression and drives interstitial fibrosis in cardiac aging [14]. Take together, these studies have favored a culprit role for obesity in premature cardiovascular aging. A number of studies further indicated the role for compromised autophagy in obesity-induced cardiovascular aging through mitochondrial injury and oxidative damage [55, 59–61]. Obesity is known to compromise autophagy in the cardiovascular system [8, 62]. Autophagy defect is also associated with cardiomyopathy and premature death [63]. Wu and colleagues reported that mitophagy preserves mitochondrial integrity and protects against

metabolic stress-induced endothelial injury [64], favoring a role for autophagy dysregulation in premature cardiovascular aging in obesity. Assessment of adiponectin levels revealed reduced adiponectin levels in young obese and old subjects, irrespective of obesity. Considering the pivotal role of adiponectin in autophagy and mitochondrial biogenesis, these findings supported a likely tie among obesity, mitochondrial dysfunction and autophagy in the obesity-induced premature cardiovascular aging [65]. It is plausible to speculate that obesity may generate a state of premature aging through mitochondrial dysfunction, oxidative stress, and apoptosis, resulting in LV dysfunction or higher vulnerability to a later insult. Obesity-related acceleration of telomere shortening is confirmed to promote premature cardiovascular aging [66] although there is little evidence suggesting involvement of autophagy in this process. However, it is noteworthy that mitochondrial and cardiac dysfunction (characteristic of premature cardiac aging) were not seen in metabolically obese individuals [67]. Obesity-induced premature aging may also be mediated through increased incidence of dementia, which is well known to be associated with impaired autophagy [68]. Being obese below the age of 65 years exhibited a positive correlation with the incidence of dementia, although the opposite finding was found in those aged 65 and over [69]. Given the close association among obesity, insulin resistance, and type 2 diabetes, it is difficult to credit those changes to obesity or to secondary metabolic changes caused by insulin resistance or diabetes.

Perhaps one puzzling issue for obesity-associated cardiovascular aging is the existence of “obesity paradox” - referring to improved survival with established CVD in obese individuals. Controversy still exists for this paradox and the survival advantage is lost in those with extreme obesity [13, 70].

b. Autophagy in insulin resistance-associated cardiovascular aging

Insulin is the major anabolic hormone with an essential role in growth, development, aging, and glucose, fat, and protein metabolism [8]. Insulin resistance is associated with cardiac and vascular dysfunction, many of which reminiscent of those found in premature aging. Insulin levels are governed by crinophagy - a lysosomal degradation mechanism of secretory granules. At low glucose levels, crinophagy is turned on to foster degradation of insulin secretory granules, while such process is inhibited at high glucose levels [71]. Longevity extension in *Drosophila* is associated with amelioration of insulin resistance [72]. Further evidence suggested declined autophagy contributes to insulin resistance in aging [73]. Hyperinsulinemia suppress autophagy and promote cardiovascular aging, while suppressed autophagy inhibits insulin signaling [8]. Reduced circulating insulin enhances insulin sensitivity in old mice and extends lifespan [74]. This is consistent with the notion that genetic downregulation of insulin/IGF-1 signaling components promotes autophagy and extends life span [55]. Mice with Atg7 haploinsufficiency are metabolically normal although these mice are prone to insulin resistance, lipid overload, and diabetes when crossed with ob/ob mice [75]. Insulin sensitization agents such as metformin display benefits on insulin signaling, metabolic profiles and retardation of aging, in association with autophagy induction [76, 77]. Many aging hypotheses proposed over the past decades converge at the point of insulin resistance. For example, the molecular inflammation hypothesis of aging is based on activities of NF- κ B signal and activation of the systemic inflammatory response in

aging when there is increased adiposity. Chronic inflammation perpetuates an insulin resistant state compromising autophagy, while the ectopic adiposity, such as lipid accumulation in liver and muscles further exacerbates, autophagy deficiency, insulin resistance and aging process [78]. In a multivariate regression model, insulin resistance emerged as an independent risk factor for increased carotid artery intima thickening (a marker for vascular aging) in obese children [79]. A recent study has indicated that inactivation of Vps34 PI 3-kinase, an integral autophagy initiating molecule, enhances insulin sensitivity and metabolism via reprogramming of mitochondrial metabolism [80], suggesting a complicated role of autophagy in the regulation of insulin sensitivity.

c. Autophagy in hypertension-associated cardiovascular aging

Aging elicits structural and functional changes in arteries mainly manifested as endothelial dysfunction, vascular remodeling, inflammation, calcification and stiffness resembling vascular alterations in hypertension [81]. On the other hand, patients with progeria suffer from atherosclerosis, suggesting a key role for vascular injury in organismal aging [81, 82]. It remains unclear how senescent vascular and endothelial cells contribute to vascular diseases such as atherosclerosis and stiffness although a number of theories were postulated such as aberrant signal transduction, oxidative stress, pro-inflammatory and pro-fibrotic transcriptional activation [83]. In salt-sensitive rats, supplementation of autophagy inducer polyamine spermidine delays the development of arterial hypertension and hypertensive heart disease. It was believed that the blood pressure-lowering effect of autophagy induction may result from improved global arginine bioavailability. In humans, high dietary spermidine intake lowered blood pressure and the overall risk of cardiovascular diseases [84]. These findings suggested spermidine as a cardiovascular- protective dietary autophagy inducer [44]. Aging is associated with high prevalence of arterial stiffness, and downregulation of the aging-suppressor protein klotho (which is known to favor autophagy) [46]. Evidence suggested that klotho deficiency-triggered arterial stiffening involves autophagy induction (possibly a compensatory response), leading to increased collagen-1 and decreased elastin levels [85]. Mitochondrial dynamics is also suggested to vascular aging as loss of mitochondrial fission protein dynamin-related protein 1 (DRP1) during senescence may attenuate endothelial cell dysfunction through mitochondrial ROS and suppressed autophagic flux. This notion was further supported by DRP1 inhibition-induced suppression of autophagic flux, premature aging and aberrant angiogenic function in young endothelial cells, the effect of which can be rescued by antioxidant N-acetyl-cysteine [86]. More evidence confirmed the role of autophagy in maintaining normal vessel wall biology and autophagic dysregulation fosters vascular aging and associated pathologies. More evidence has linked autophagy to a number of vascular processes including angiogenesis and calcification. Likewise, pathological insults including oxidized lipids and β -amyloid may stimulate autophagosome formation in vascular and endothelial cells. These findings further implicate the pivotal role of autophagy in vascular aging pathologies including atherosclerosis and pulmonary hypertension [34]. In a recent study, Tucsek and colleagues reported that synapse loss and impairment in synaptic plasticity in hippocampus seen in hypertension mimics the aging phenotype and suggests possible contribution of synaptic plasticity to the pathogenesis of vascular cognitive impairment [87] although a direct role of autophagy in such process needs to be confirmed. Along the same line, hypertension may be

associated with accelerated loss of telomere length in human [38] although little information is available for the role of autophagy.

d. Autophagy in diabetes- and pancreatic defect-associated cardiovascular aging

Diabetes shortens life span, and promotes pathological changes in the heart and vasculature [88]. It is believed that glycogen from dietary glucose accelerates aging and limits longevity in an oxidative stress-dependent manner [89]. Common cardiovascular risk factors including high HAlc levels are likely major factors predicting early cardiac dysfunction and remodeling in type 1 diabetes [90]. Patients with type 2 diabetes often exhibit similar adverse cardiovascular risk profiles including diastolic dysfunction, higher LV mass and LV concentric remodeling [91]. Although diabetes mellitus exerts more impaired LV systolic and diastolic function for all BMI categories, diabetes seems to produce lesser cardiac dysfunction as opposed to obesity [92]. In addition, diabetes produces additive unfavorable cardiovascular sequelae in conjunction with increased BMI. Autophagy dysfunction is well established for diabetes, reminiscent of aging and dementia [93]. Cardiac autophagy initiation was suppressed (Atg12, the Atg12-Atg5 complex and AMPK signaling) in type 1 diabetes (streptozotocin and OVE26-diabetic models) [8]. To the contrary, late lysosomal degradation was suppressed in hearts from type 2 diabetes [94]. The diabetes-induced loss of autophagy contributes to decreased aggregate clearance activity and early onset of cardiovascular aging. Pancreatic autophagy also determines diabetes-accelerated cardiovascular aging. Given the stimulatory role of autophagy on autoimmune process [95], inhibited autophagy is supposed to protect pancreatic β cells, limit diabetes progression and cardiovascular complications. However, genetic ablation of Atg7 in pancreatic β cells triggered islet degeneration and impaired insulin secretion [8], suggesting a role of autophagy in normal cellular architecture and function. It is noteworthy that cardiac autophagy was elevated in fructose-induced type 2 diabetes, in conjunction with pathologic remodeling of the heart, consistent with upregulated autophagy in type 2 diabetic pancreatic β cells [8]. Munasinghe and colleagues reported that excessive autophagy injured myocardial cells and cardiac function [96]. However, autophagy was decreased in db/db type 2 diabetic nephropathy. Activation of CaMKK β -LKB1-AMPK signaling cascade attenuated diabetic nephropathy in db/db mice by modulation of autophagy [97]. Diabetes may also impair stem cell regeneration capacity to foster premature aging. Recent evidence from Kornicka and coworkers found that mesenchymal stem cells from type 2 diabetic patients were dysfunctional as a result of oxidative stress and dysregulated autophagy, thus limiting their therapeutic potential in aging [98].

e. Autophagy in fatty liver disease and dyslipidemia-associated cardiovascular aging

Nonalcoholic fatty liver disease (NAFLD) imposes a heavy burden of hepatic and extra-hepatic complications in the elderly [20]. With the high prevalence of obesity and diabetes in the aging populations, NAFLD-related morbidity and mortality are expected to continue rising in the United States although the mechanism remains elusive. One explanation is the involvement of fibrosis as the risk of hepatic mortality rises exponentially with the increase in fibrosis stage [99]. Mitochondrial integrity also contributes to the interplay between NAFLD and aging. Hepatic mitochondrial respiration deteriorates with aging in NAFLD [100]. Dampened mitophagy and lipophagy in NAFLD leads to reduced ability to clear

defective mitochondria and excess lipids, in a manner similar to premature aging [8]. High fat diet feeding was shown to downregulate autophagy and promote activation of NLRP3 inflammasome [101], a known aging inflammatory marker. Recent evidence also suggested that the master regulator of lysosomal function transcription factor EB (TFEB) confers hepatoprotection against diet-induced steatosis and extends lifespan [102]. Certain longevity gene may participate in NAFLD-induced premature aging as NAFLD promotes the rise of the Indy ("I am Not Dead, Yet"), the reduction of which promotes longevity. Ablation of the mammalian homolog of Indy encoding a plasma membrane-associated citrate transporter in the liver protects against high fat diet- and aging-induced obesity and hepatic steatosis [103, 104]. In a recent study, Pesta et al examined the impact of selective hepatic knockdown of Indy on lipid and glucose metabolism using a chimeric anti-sense oligonucleotides and revealed reduced plasma insulin, and triglycerides along with improved hepatic steatosis and insulin sensitivity [105]. NAFLD may also promote premature aging through promoting other metabolic risk factors such as telomerase length loss and hypertension [66]. In a well-controlled cross-sectional study, NAFLD was found to be associated with high prevalence of hypertension independent of other metabolic risk factors [106]. More in depth characterization of mechanisms of NAFLD should help to elucidate the most accurate diagnosis and therapeutics for individual elderly patients [107].

f. Impact of neurohormonal and circadian dysregulation on cardiovascular aging

Metabolic diseases are associated with neurohormonal defect [activation of sympathetic adrenergic, rennin-angiotensin-aldosterone system (RAAS) and insulin-IGF-1] and neurodegenerative changes, leading to dysregulated proteostasis, inflammation, oxidative stress, arterial stiffness and premature cardiovascular aging. These neurohormonal dysregulation and neurodegenerative changes directly compromise autophagy to favor impaired aggregate clearance. It is generally considered that acute activation of adrenergic and RAAS system may favor autophagy while their long-term overactivation dampens autophagy [108]. Much progress on neuroendocrine-directed therapies, such as those targeting RAAS and natriuretic peptides, has been achieved however the role of autophagy in such therapies remains elusive. Modulators of autophagy and pro-inflammatory NF- κ B exhibit potent neuroprotective effects in pathological settings and may benefit aging process [36]. Protein aggregates such as lipofuscin and β -amyloid are confirmed to contribute to age-related impairment of proteostasis and degenerative diseases such as Alzheimer's disease [109]. Not surprisingly, enhanced autophagy has shown promises in the management of neurodegenerative disease and related cardiovascular anomalies. Moreover, circadian clock genes have been shown to limit or remove disability and death associated with neurodegenerative disorders and premature aging. Circadian genes share a common link to the longevity gene Sirt1 and mTOR, offering governance of autophagy to limit cognitive loss and neuronal injury [110]. More recent evidence suggests that changing the "circadian cycle" of feeding with inter-meal fasting with caloric restriction may drive energy expenditure, lower lipid levels, suppress gluconeogenesis, and prevent age/obesity-associated metabolic defects [111].

FUTURE PERSPECTIVES, CHALLENGE AND CONCLUSION

Premature cardiovascular aging is a stress-induced deteriorating process, aberrantly activated by metabolic stress including obesity, hypertension, insulin resistance and type 2 diabetes [3, 18, 20, 65]. Metabolic stress-associated “failure” in autophagy aggregate clearance mechanism appears to govern the transition of healthy state of cells, tissues or organs into a pre-senescent state with overt pathology. Various benefits have been confirmed for induction of autophagy in lifespan or aging-related complications in both clinical and experimental settings [44]. Nonetheless, contradictory observations still exist with regards to the protective versus deleterious role of autophagy induction in certain contexts of aging or metabolic stress (Text Box 3) [26]. Future strategies may be engaged on autophagy regulation to retard or halt aging- associated cardiovascular anomalies (Text Box 3). Continued work with development and circadian clock genes as well as pharmacological agents targeting metabolic disease should offer new prospects and hope for the development of novel strategies for the management of premature aging (Outstanding Questions). These innovative approaches may shed some promises towards to significantly limit disability and death from these devastating aging disorders [110].

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| Pathophysiological changes in cardiac and vascular aging

Cardiovascular aging is mainly manifested as a cascade of pathophysiological changes including myocardial remodeling, deteriorated cardiac reserve and contractile function, arterial stiffness, decreased vascular compliance and endothelial injury [2, 18]. In cardiac aging, cardiac pump contractile capacity deteriorates rapidly including elevated left ventricular (LV) wall thickness and chamber diameter, decreased contractility, prolonged diastolic filling, loss of compliance of ventricular wall and coronary vasculature [2, 3]. In vascular aging, vascular compliance decreases, vascular remodeling (calcification and interstitial fibrosis) and endothelial injury develop to impose increased afterload for the heart to initiate early adaptive processes followed by transiting the heart from a compensatory to a decompensatory stage to interrupt pump function [3].

| Mitophagy in cardiovascular disease and aging

Mitochondria are the powerhouse in the cell to generate most of the energy through oxidative phosphorylation. To ensure a healthy population of mitochondria for ATP production, the unhealthy, unwanted and damaged mitochondria are eliminated primarily via process known as mitochondrial autophagy or mitophagy [112]. Depolarized or superfluous mitochondria need to be labelled for target degradation. Signals from damaged mitochondria to initiate mitophagy involves reduced ATP production, reactive oxygen species (ROS), and mitochondrial permeation transition pore (mPTP) opening [39]. Two types of selective mitophagy exist including 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)]. Upon mitochondrial depolarization, Pink1 is recruited to the outer mitochondrial membrane where it phosphorylates ubiquitin and other mitochondrial outer membrane proteins, to facilitate Parkin translocation. BNIP3 and BNIP3L/Nix interact directly with LC3 to initiate mitochondrial removal. Fundc1 is located on the outer mitochondrial membrane with a binding domain for LC3 and governs mitochondrial engulfment [39, 113]. Compromised mitophagy is found in various cardiovascular diseases and aging, resulting in the accumulation of protein aggregates and damaged mitochondria, unfavorably influencing mitochondrial function, metabolism, lifespan and healthspan [39, 55, 113]. Induction of mitophagy such as using spermidine extends lifespan, preserves in metabolic and cardiovascular homeostasis [39, 44]. Mitophagy might be both a cause and effect of premature cardiovascular aging, and might create a vicious cycle of mitochondrial deterioration in aging and aging-related diseases.

| Major inconsistencies and challenges for autophagy in aging

It remains unclear whether aging compromises autophagy homeostasis prior to the decline of overall cardiovascular and metabolic function or vice versa. Whether altered autophagy with age is a direct consequence of biological aging process or an indirect effect of metabolic derangement such as lipid spillover with aging. Expression of longevity and/or senescence genes might not be coordinated with autophagy activity. It remains to be determined for the role of aging- and metabolic stress-related post-translational modifications of autophagy proteins, to better understand the interplay

between aging and metabolic diseases. The protein levels required to induce autophagy or mitophagy might not be safe to administer in vivo due to off-target effects and toxicity. Clinical translation may be challenging for the development of autophagy modulators in the management of cardiovascular aging (off-target effect and toxicity). Although some metabolic drugs such as metformin exhibits anti-aging effect in association with autophagy induction, it remains unclear whether the improvement in metabolic and/or endocrine function with newer metabolic pharmacological agents [such as glucagon-like peptide-1 (GLP-1) analogues or sodium-glucose cotransporter-2 (SGLT2) inhibitors] is due to regulation of autophagy, and whether these agents benefit cardiovascular aging?

TRENDS:

- ✓ Population-based studies, clinical trials, and experimental data have depicted a close relationship between age-related chronic diseases such as insulin resistance, type 2 diabetes, hypertension, obesity, atherosclerosis, and metabolic dysfunction.
- ✓ Metabolic diseases impose stress on cardiovascular function, fostering premature cardiovascular aging.
- ✓ Proteotoxicity due to poor protein quality control in particular autophagy contributes to the pathogenesis of metabolic dysregulation and aging.
- ✓ Autophagy delays aging, and prolongs lifespan, exhibiting promises for the prevention and therapeutics of metabolic diseases.
- ✓ Does aging compromise autophagy homeostasis prior to the decline of overall cardiovascular and metabolic function or vice versa? Understanding these sequences should be instrumental in guiding the clinical therapy for metabolic diseases associated with aging?
- ✓ Do changes in autophagy function under various metabolic stresses (genetically predisposed or environmental factors) affect the premature aging differently? Does disparity in metabolic stress-induced changes in autophagy affect premature aging in an organ specific manner? Understanding the difference in autophagy changes under various metabolic stress or organs should help us to assess the disparity in organ aging.
- ✓ Does improvement in metabolic and/or endocrine function using certain drug types (for example, GLP-1 analogues or SGLT2 inhibitors) help to retard aging directly or indirectly through manipulation of autophagy?
- ✓ Is it safe to administer modulators of autophagy in the elderly considering the potential off-target effects and toxicity of these drugs?

Figure 1:
Schematic diagram displaying metabolic and cardiovascular effects of obesity. RAAS: renin-angiotensin-aldosterone system; FFA: free fatty acids.

Figure 2:

Schematic diagram displaying various contributing factors for metabolic disease in the complex pathophysiology of premature cardiovascular aging process. Metabolic risk factors likely compromise aggregate clearance ability through autophagy/mitophagy, leading to compromised insulin signaling (insulin resistance can also serve as a trigger for metabolic stress), oxidative stress, pro-inflammatory response and ultimately mitochondrial injury. Various aspects of cardiac and vascular aging are summarized here in response to mitochondrial injury. Telomere length loss may also contribute to premature cardiovascular aging under metabolic stress although it is merely associated with autophagy failure at this stage.