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Minireview

Obesity is a common soil for premature cardiac aging and heart diseases - Role of autophagy☆

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ABSTRACT

The advance in medical technology and healthcare has dramatically improved the average human lifespan. One of the consequences for longevity is the high prevalence of aging-related chronic disorders such as cardiovascular diseases, cancer and metabolic abnormalities. As the composition of aging population is raising in western countries, heart failure remains the number one cause of death with a more severe impact in the elderly. Obesity and aging are the most critical risk factors for increased susceptibility to heart failure in developing and developed countries. Numerous population-based and experimental data have depicted a close relationship between the age-related diseases and obesity. There is an overall agreement that obesity is causally linked to the development of cardiovascular disorders and severe premature cardiac aging. Accumulating evidence indicates that autophagy plays an important role in obesity, cardiac aging and diseases. In this review, we will focus on the role of autophagy in obesity-related cardiac aging and diseases, and how it regulates age-dependent changes in the heart.

1. Introduction

The prevalence of obesity is increasing worldwide and has become a major public health problem during the past decades [1]. Obesity has been recognized as a significant risk factor of cardiovascular diseases (CVD) and severe premature cardiac aging. The National Health and Nutrition Examination Survey (NHANES III, 1988–1994; NHANES continuous, 1999–2010) revealed reduced lifespan with increased body mass index (BMI) (reduce life expectancy at the age of 40 by 0.9 years), which was responsible for 186,000 excess deaths in 2011 [2]. More epidemiological studies confirm the tight association between obesity and reduced lifespan [3–6]. Obesity is found closely related to premature cardiac aging and high-risk factor in young patients, contributing to an increased risk for heart failure with aging [7]. Inflammation, oxidative stress, mitochondrial dysfunction and autophagy disorder caused by obesity generally accelerate the development of cardiac aging and heart diseases (as depicted in Fig. 1) [8]. As the increasing age, the heart trends to display an increased accumulation of lipid and decreased number of cardiomyocytes. Premature aging is commonly associated with the increasing prevalence of obesity, while both obesity and aging are comorbidities leading to severe CVD and increased risk of death [8]. Both obesity and aging are tied with an increased risk for cardiac surgery, and thus, it is interesting to underline the contemporary mechanisms related with obesity-induced premature aging and associated cardiac dysfunction ultimately leading to heart failure [9].

Autophagy is the process by which cellular components are degraded and recycled within the cell. Increasing lines of evidence show that autophagy plays a crucial role in obesity and heart aging and during stress [10,11]. In obese patients, obesity disrupts autophagosome maturation probably at the step of autophagosome–lysosome fusion, although it promotes the initiation and accumulation of autophagy correlating with the degree of obesity [12]. Inhibition of autophagy in the heart induces premature cardiac aging which is generally accompanied by cardiac hypertrophy, fibrosis, accumulation of misfolded proteins and impaired mitochondrial function [13]. These

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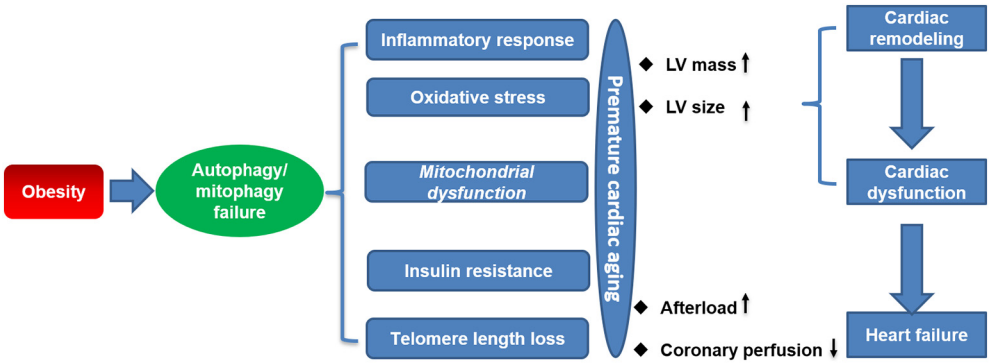

Fig. 1. Obesity is a common soil for cardiac aging and heart diseases. Obesity generally causes inflammatory response, oxidative stress, mitochondrial dysfunction, insulin resistance and telomere length loss through disrupting the autophagy and mitophagy which significantly contribute to the development of cardiac aging and heart diseases.

findings raise the emerging possibility that autophagy may play an essential role in combating the adverse effects of obesity-related cardiac dysfunction. In this review, we discuss the role of autophagy in obesity-induced cardiac aging and diseases.

1.1. Impact of obesity on cardiovascular of aging and heart diseases

In the United States, heart disease is still the number one cause of death and approximately 790,000 people get heart attacks each year and of those around 14.4% will die [12]. Obesity is one of the key factors that risk premature severe cardiac aging and obesity-associated cardiac dysfunction. In adults, obesity is commonly defined as BMI > 30 kg/m^2 and has become a global epidemic nowadays, widely recognized as a major risk factor for CVD and other chronic diseases [13,14]. Among the CVD patients, the average BMI exceeds 25 kg/m^2 and more commonly exceeds 30 kg/m^2 in clinical trials, and over 80% of patients with CVD are either overweight or obese [15]. The active link between obesity and CVD incidence and CVD mortality are not only based on point assessment but also be proved by several cohort studies to have a clear dose-response pattern with CVD mortality. For example, the Framingham Cohort study demonstrated that the risk of CVD mortality significantly raised 7% for every two years additionally lived with obesity [16]. Obesity is reported to affect cardiac geometry and function which leads to the remodeling structure of the heart and thus decreasing cardiac function [17]. Facing the stresses of obesity, the substrate utilization of cardiomyocytes could be gradually transferred from glucose to fatty acid, the function of mitochondria could be impaired by increased oxidative stress, apoptosis and accumulation of toxic lipid intermediates [18].

Aging is another risk factor for CVD which is evidenced by the prevalence of heart failure increases with aging: the people who live to age 40 at least have 20% lifetime risk of developing cardiac disease. In particular, the prevalence rate of CVD increases almost 10% with ten years increment in age from 60 (70% prevalence) to 80 (90% prevalence) [12]. Aging and obesity severely deteriorate the structure and function of the heart in a similar manner: adequate studies in human and animal models on aging have shown that aging increases in the prevalence of LV hypertrophy, a decline in LV systolic and diastolic function [19]. Obesity-related heart disease contributes to premature death and the study of obesity in children shows that obesity accelerates the heart aging. The significant cardiac remodeling and dysfunction are observed as young as an age of 8 in the obesity condition [20]. Thus, obesity plays a vital role in the accelerated aging and heart failure.

2. Mechanisms of obesity-related cardiac aging

Age-related CVDs are characterized by decreased contractility, impaired diastolic function, and atrium dilatation which is a rapidly increasing problem worldwide. During the aging process, both the morphological and functional alterations result in these diseases of the heart [21]. Obesity accelerates the aging process, and it is the key factor that risks premature severe cardiac aging and obesity-associated cardiac dysfunction [22]. It is reported that a large decrease in life expectancy and an increase in early mortality were associated with obesity [23]. With the age increases, obese patients are suffering from an increase in age-associated disease prevalence suggesting a premature aging phenotype [24]. The common features – such as impaired immunity, oxidative and inflammatory stress and mitochondrial dysfunction – have been revealed for both obesity and advanced aging [25]. Notably, adequate evidence indicates that the impaired or declined autophagy in the degradation system has a vital impact on senescence development with the cardiovascular system. Herein, we review the mechanisms of obesity-related cardiac disease.

2.1. Inflammation and aging

Permanent inflammatory state has been associated with both obesity and premature aging. In most of the elderly population, there is a chronic low-grade raise in the levels of steady-state serum proinflammatory cytokine. In contrast, the aging process declines the acute inflammatory response against pathogens which decreases the susceptibility to infections [26]. These results elicit that aging could induce and sustain the chronic inflammation (inflammaging). In addition, adipose tissue from obese individuals contains higher numbers of senescence-associated secretory proteins (SASP) compared to lean age-matched controls [27,28]. SASP members include interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), several matrix metalloproteases (MMPs), and the protease inhibitor plasminogen activator inhibitor-1 (PAI-1), which collectively support the inflammatory state of aging [29]. The mechanism of inflammaging has been proposed to be the chronic stimulation of immune cells by a persistent cytomegalovirus infection [30]. On the contrary, age-associated chronic inflammation has been involved in the alteration of innate immune functionality. It is also found that a premature immunosenescence is associated with the high-fat intake during adolescence diet [25].

2.2. Oxidative stress and aging

Oxidative stress causes chemical modification (such as the oxidation of proteins, nucleic acids, and lipids) which ultimately leads to the cell damage and contribute to the diseases commonly found in aged and obese individuals, such as diabetes mellitus, CVDs, and cancer [31–33]. The oxidative stress increases with aging and induces gradual mitochondrial damage and dysfunction accompanied by mitochondrial-DNA (mt-DNA) mutations. Impaired mitochondrial with deficiency mosaic respiratory chain has been found in different aging organs including heart [33]. Besides damaged mitochondria, oxidative stress also promotes telomere attrition [33]. ROS is involved in the telomere shortening machinery which affects the guanine in the 5′-TTAGGG-3′ telomere repeat sequence. In addition, decline of intracellular NAD + and decreased sirtuin activity in the heart, lung, liver and kidney in

female rat can also lead to ROS-induced DNA damage which promotes cellular senescence [34].

2.3. Mitochondrial dysfunction and aging

Mitochondria are fundamental for meeting the high energy demands of the myocardium which plays a determining role in the function and survival of cardiomyocytes [27]. Mitochondrial dynamics have critical roles in aging, and their impairment represents a prominent risk factor for myocardial dysfunction. Mitochondrial ROS induces an accumulation of mtDNA mutations and loss of mitochondrial function. It plays a fundamental role in loss of cardiomyocyte function and, therefore, cardiac aging. Mitochondrial deacetylase sirtuin (SIRT)3 contributes greatly to the prevention of redox stress and cell aging. Li and colleagues confirmed SIRT3 expression levels were significantly lower in the myocardia of aged mice compared with young mice, and the activity of mitochondrial manganese superoxide dismutase (MnSOD) and peroxisome proliferator-activated receptor γ coactivator (PGC)-1α was reduced in the aged heart. In the myocardium of SIRT3 −/− mice, mitochondrial protein dysfunction, enhanced oxidative stress, and energy metabolism dysfunction are the common features of aging. Therapeutic activation of SIRT3 and improved mitochondrial function may ameliorate the symptoms of cardiac aging [35,36].

2.4. Autophagy and obesity-related cardiac aging

2.4.1. Overview of autophagy

Autophagy is responsible for clearance of intracellular substances through lysosomes or vesicles [37]. Initially, an autophagosome is formed around damaged organelles or unused proteins, which begins with the establishment of phagophore. Endoplasmic reticulum, plasma membrane and mitochondria are all likely Lipid sources for the phagophore membrane [38]. The formation of the autophagosome is initiated by the class III phosphoinositide 3-kinase (PI3-K) complex, which is activated by the Beclin 1/Atg6/vacuolar protein sorting (VPS) 34 complex [39]. Then, two ubiquitin-like conjugation systems were involved in the elongation of the phagophore, Atg5-Atg12 and LC3 (microtubule-associated protein 1 light chain 3), and the closure of the isolation membrane was accompanied with the binding of Atg5-Atg12 complex to LC3 [40]. During this process, Atg5-Atg12 oligomerizes with Atg16 to form Atg5-Atg12-Atg16 complex. Cytosolic LC3 is cleaved into the soluble form of LC3 known as LC3-I by ATG4 and subsequently the autophagosome is converted into the autophagic vesicle-associated form represented as LC3-II by ATG7 and E2-like enzyme ATG3, and then mature LC3-II accumulates in the autophagosome membrane and combines with specific adapter proteins or receptors that are resided on the cargo [41]. Finally, the cargo is enclosed by the autophagosome and fused with a lysosome, where the contents are degraded by lysosomal enzymes. The resultant products are recycled for energy as metabolic substrates after being released back into the cytosol [38].

Autophagy is usually classified into three types: microautophagy, chaperone-mediated autophagy, and macroautophagy. The first type of Macroautophagy (hereafter referred to as autophagy) could be further divided into mitophagy and lipophagy [42], which plays a key role in the broad regulation of cellular quality control processes and adaptation to stress. It was originally believed as a non-selective mechanism for the constitutive process; however, later it is well recognized as a specifical mechanism that target protein aggregates organelles such as endoplasmic reticulum, mitochondria and bacteria in different mammalian cells [36]. The other two types, chaperone-mediated autophagy and macroautophagy, are participated in more specialized cellular functions.

2.4.2. Autophagy in cardiovascular physiology

Autophagy has a vital role in the heart [43]. Because cardiac myocytes are terminally differentiated and unable to renew themselves, they rely on autophagy to maintain their viability and functionality. In the heart, autophagy constitutively keeps at a basal level under normal physiological conditions to perform housekeeping functions, such as degrading aged proteins and impaired organelles, to maintain cardiac function and morphology [44]. Dysregulated or impaired autophagy in cardiaomyocytes is deemed a primary trigger for cardiac dysfunction. Cardiomyocytes adapt to changes in nutritional and energy demands during stress according to increasing autophagic activity. Cardiac myocytes have a high requirement for ATP, which is supported by a large population of mitochondria and a steady supply of oxygen. Increased autophagy can help maintain ATP levels to sustain the contractile force of cardiomyocytes [45].

Because cardiac myocytes require high energy which is dependent on mitochondria for ATP to sustain contraction, impaired mitochondrial biogenesis is considered as an early signal in heart failure which contributes to cardiac aging [46]. The autophagy special for the sequestration and degradation of mitochondria is also called mitophagy which is essential for cellular homeostasis, especially in the myocardium [47]. As the impaired mitophagy may cause the accumulation of dysfunctional mitochondria, the deregulated mitophagy is the main source of ROS (Reactive oxygen species). ROS, in turn, will damage mitochondria proteins and DNA, resulting in more dysfunctional mitochondria, further promoting the cycle [48]. Therefore, when mitophagy is impaired, the accumulation of dysfunctional mitochondria is increased, which results in excessive ROS in mitochondria and subsequently contributes to mitochondrial dysfunction, cardiac aging and myocardial injury [46,49]. Besides, the impaired mitochondrial clearance also has other adverse effects, such as increased inflammation, decreased contractile reserve, reduced tolerance to stress injury [50].

Autophagy and mitophagy have been shown to be altered in various cardiac disorders including heart aging. Their significance in the healthy heart has also been featured in several studies. For instance, mice with cardiomyocyte-specific deficiency in Atg5 expression (autophagy related 5) developed cardiac dysfunction and premature death accompanied by mitochondrial misalignment and disorganized sarcomere [11]. Overexpression of Parkin, a vital regulatory factor of mitophagy, rescues the age-related deleterious effect in cardiac function [50], whereas Park2-deficient mice exhibited constant degradation of mitochondrial metabolic functions and impaired recovery of cardiac contractility [51].

2.4.3. Roles of autophagy in longevity in animal models

Besides the role of protection in heart failure, recent genetic evidence suggests that autophagy plays a critical role in the elongation of animal lifespan. In Drosophila and mice, it is found that the knock-out or mutation of autophagy genes such as Atg8a gene (autophagy-related 8a) and Atg5 (autophagy-related 8a) are significantly related with the lifespan [52]. Autophagy induction using mTOR inhibition extends lifespan in multiple species including yeast [53], *C. elegans* [54], and Drosophila [55], and mice [56]. Recent findings from Levine and colleagues noted alleviated premature aging, and improved longevity in mammals with disruption of the Beclin1-Bcl-2 autophagy complex (which inhibits autophagy) [57]. Although several mechanisms may lead to life extension, the intracellular recycling process of autophagy is a major life-span determinant in several longevity models. The basal level of autophagic activity is elevated in many longevity paradigms and the activity is required for lifespan extension [58]. Importantly, some interventions of autophagy have been shown to extend the lifespan in many animal species which will be discussed in the following section.

2.4.4. Autophagy dysregulation in obesity-related cardiac aging and heart diseases

Obesity has been generally considered to dysregulate autophagy and the increasing number of autophagosomes has been found in different cultured cells and human tissues [59,60]. In adipose tissues, obesity can lead to the defective regulation of autophagy and it is suggested that autophagy failure and insulin resistance are independent outcomes of obesity. In the liver, the obesity impairs autophagy with decreased expression of autophagy genes which promotes ER stress [61]. Autophagy is pivotal for the hemostats of cardiac system, and it has been clarified have a role in obesity-induced cardiac disease [10,62]. As the age increases, the autophagy and mitophagy failures elevate the intracellular aggregates and disturb the homeostasis. Cardiac autophagy is deregulated in animals with high-fat diet (HFD)-induced obesity and metabolic syndrome. In obese patients, obesity disrupts autophagosome maturation probably at the step of autophagosome–lysosome fusion, although it promotes the initiation and accumulation of autophagy correlating with the degree of obesity [10]. Even though the high level of autophagy might be deleterious in specific cardiac stress conditions, more and more significance is adding to the role of autophagy in the promoting of cardiomyocyte survival with an adaptive mechanism. Autophagy is found to serve as a protective role in lipotoxic condition, for example, in the model of mice, the HFD induced obesity was found to compromise myocardial geometry and function by disrupting the process of autophagy and these adverse effects are rescued by Akt2 knockout which was facilitating the maturation of autophagy [62,63]. It has been proposed that impairment of autophagy may also reduce the mitochondrial function and oxidative in obesity. The mitochondria function is changed by lipotoxicity from obesity which facilitates the formation of active lipid mediators and eventually changes cardiac metabolism and cardiac function [18,64–67].

In the regulation of cardiomyocyte survival and death during obesity, autophagy has also been proved to play a critical role [59–61,68]. In cardiomyocytes, accumulation of damaged proteins, DNA, and cellular organelles contribute to the aging process [69]. Autophagy also promotes the degradation of the long-lived proteins and organelles which is essential for the heart homeostasis in the aging process [10,70,71]. During aging, the autophagy is aggressively deregulated, and this decline of autophagy is closely related with aging-induced cardiac abnormalities [61,72]. The mutation of genes involving in the autophagy pathway including Atg1, Atg7, Atg18, and Beclin1 is proved to decrease the lifespan of the nematode *C. elegans* and budding yeast [73,74]. In worms, with prolonged starvation, these autophagy-related genes have also been found promoting longevity by alleviating age-associated pathologies, including mitochondrial and cardiac dysfunction [75,76]. Recently studies in mice model strongly supported that autophagy is a critical protective cardiac aging during obesity stress [77]. Several researchers reveal that fibroblast growth factor-21 (FGF21) increase the longevity through by promoting autophagy which contributes to lipid accumulation and cardiac disorder [78–80].

The decreased autophagosomes number and lysosomal clearance have been found as evidence of autophagy dysregulation in the obesity [81,82]. The levels of LC3-II are affected by both autophagosome formation, and autophagosome clearance and impairment of autophagy are usually accompanied by a massive accumulation of p62/SQSTM1 followed by the collection of ubiquitinated protein [83,84]. Recent studies showed genetic obesity-(ob/ob) mice- has reduced LC3II levels both at baseline and after inhibition of lysosomal function by lysosomal inhibitors, indicating the altered autophagy is not at their clearance step, but at the level of autophagosome formation as evidenced [85]. However, in palmitate-treated rat H9C2 cardiomyocytes, the autophagosome clearance was suppressed by attenuating lysosome activity which was restored by inhibition of Nox2 [86]. In a model of high-fat diet (HFD)-induced obesity, autophagic flux in the heart is altered by reduced LC3II both at baseline and after using -lysosomal inhibitors, suggesting obesity modified autophagy at the level of autophagosome for mature but not at their clearance step [85]. Besides, HFD reduced the number of autophagosomes with and without a lysosomal inhibitor [60] illustrated the impaired cardiac autophagy in the metabolic syndrome. The reduction of autophagosome number is further confirmed in other HFD studies in mouse hearts [82,87].

Mammalian target of rapamycin (mTOR) signaling - a potent negative regulator of autophagy- is the primary mechanism regarding with the mice with obesity induced heart failure and cardiac aging [88–93]. mTOR activation by HFD which disrupted the autophagosome maturation has been found rescued by the AKT2 Knockout [94]. The mtDNA mutation stimulates mitochondrial autophagy in erythroid cells which are found downregulated by aging [95]. Mitophagy could also be prevented by the activated mTOR in HFD induced obesity, and the damaged mtDNA then initiate a feed-forward mechanism that causes rapid accumulation of dysfunctional mitochondria and cell death. 5′-AMP-activated kinase (AMPK)–mTOR-autophagy signaling cascade plays a favored role in fat diet intake induced changes in myocardial autophagy. The regulation of autophagy by AMPK is finely controlled by the energy status and the levels of AMPK is downregulated in HFD-induced cardiac response [37,60,90,92,94,96–99]. The phosphatase-1B (PTP1B) knockout is found to protect HFD-induced cardiomyocyte contractile anomalies through the elevated level of AMPK, and pharmacological inhibition of AMPK disengaged protection of PTP1B [100]. It is still not fully clear that how autophagy regulates the aging process, longevity, and cardiac functions. mTOR pathway is one essential signal pathway that well known in regulating autophagy in longevity and aging. In aged hematopoietic stem cells, the mTOR pathway and aging are found tightly related. The activation of mTOR trends to worse aging phenotypes in young hematopoietic stem cells and inhibition of mTOR pathway is shown to extend lifespan in multiple species. Besides, many other life span regulation genes have been found, such as FOXO transcription factors, insulin, IGF-1, and sitruins [101].

3. The intervention of obesity-related cardiac aging and heart diseases targeting autophagy

3.1. Voluntary exercise and calorie restriction (CR)

Voluntary exercise has numerous beneficial effects on human health, along with reducing the risks for CVD, in part, by enhancing autophagy [101,102]. Regular exercise contributes to the prevention of CVD have been demonstrated by the various study [101,102]. The autophagy signaling induced by exercise including BCL2, Beclin 1, ATG7, LC3BII, Atg12 and p62/SQSTM1 in cardiac muscle [87,103]. For example, voluntary exercise has been revealed to enhance levels of autophagy and ameliorate CVD in ATG7 overexpression mouse model which increases levels of basal autophagy. Inconsistent with this, the content autophagy is found increased with exercise training evidenced by the upregulated macroautophagy markers LC3BII, Atg12, p62/SQSTM1 and phospho-ULK1 (S555) in the heart and positively impacts cardiovascular function and extends survival [103]. The autophagosome (GFP–LC3 puncta) number has also been found increased after 30 and 80 min (~300 and 900 m) of running in both skeletal and cardiac muscle [104]. It may be concluded that the beneficial effect of exercise on the heart, in part at least, mediated through the activation of autophagy and consequent amelioration of protein aggregation.

CR is a dietary intervention with the potential inducer of autophagy which increases autophagy in both young and aged hearts [105]. In the dietary-induced obese mouse model, caloric restriction reveals more beneficial effects than the exercise in dietary-induced obese mice [106]. Besides, various researchers have shown the increasing autophagy in cardiac tissue and the advanced role of CR for lifespan extension [107–111]. Therefore, CR could represent an alternative therapeutic option for the aged and failing heart and CR may also promote telomerase activity, stimulate autophagy, and rescue against diastolic

dysfunction in diabetic hearts [105,112].

mTOR is a leading target for antiaging interventions which is the nutrient response pathway. AKT and AMPK are the main regulators in mTOR signaling pathway and CR is found to extend lifespan and confers healthspan by inhibiting this pathway [118]. The increasing in nutrient has been proved to stimulate AKT-mediated activation of mTOR, but suppresses AMPK function. On the other side, the energy deprivation or CR activates AMPK [112]. Anyhow, CR cannot be widely adopted in humans as it is difficult to maintain long-term CR in modern society and there are potentially dangerous CR side effects such as hypotension, infertility, sarcopenia, depression, and emotional deadening. Therefore, Pharmacological intervention should be considered as another strategy for the therapy of obesity-induced heart failure and cardiac aging [9].

3.2. Pharmacological intervention

As mentioned above, pharmacologic induction of autophagy is a more desirable option compared with the lifestyle intervention. As discussed in previous sections, mTOR inhibitor enhances autophagy in the failing heart and elongate the longevity in mice [114–117]. Thus, the mTOR inhibitor rapamycin is an emerging candidate as an anti-aging therapeutic agent and is known to increase the level of autophagy in heart failure and aging heart [112,118–120]. Besides rapamycin, the Toll-interacting protein (Tollip), a critical innate immune molecule, has also been involved in the fusion of autolysosome [112,121,122].

It is found that rapamycin-treated mice have a lower incidence of myocardial nuclear atypia in the aged myocardium with abnormalities of nuclear size and chromatin conformation [114,116,117,120,123]. Important to note that, however, Tollip has also been reported to promote inflammation and apoptosis in the heart after myocardial infarction [121]. What's worse, many other undesirable side effects have also been raised such as testicular degeneration and cataracts [120], insulin resistance [120], glucose intolerance and hyperlipidemia [124]. Thus, further study is needed to clarify the function of this protein in the heart. AMPK is another target for intervening in the autophagy in heart disease. Plenty of evidence have shown that autophagy plays a significant metabolic role in glycogenolysis (glycophagy) and lipolysis (lipophagy) [125,126]. However, it is still not always clear whether AMPK is mediated by these agents directly or not. Similar with Tollip, much more effort still needs to be focused on demonstrating the molecular mechanisms of AMPK activators and on validating the possible side effects for these agents [127].

4. Summary and conclusion

There is an increasing need for the understanding of the correlation between obesity cardiac aging and CVD. Given that obesity includes a cluster of cardiovascular risk factors, it is not surprising that patients with obesity are more susceptible to cardiac aging and functional damage. Autophagy plays an important role in obesity, cardiac aging and heart diseases. In cardiomyocytes, accumulation of damaged proteins, DNA, and cellular organelles contributes to prematured aging process [69]. Autophagy has an essential role in the clearance of these damaged proteins and organelles which is crucial for the heart homeostasis in the aging process. Recently studies in mice model strongly supported that autophagy is a critical protective cardiac aging during obesity stress [77]. In obese patients, obesity disrupts autophagosome maturation probably at the step of autophagosome–lysosome fusion [10]. Inhibition of autophagy in the heart induces premature cardiac aging which is generally accompanied by cardiac hypertrophy, fibrosis, accumulation of misfolded proteins and impaired mitochondrial function [11]. Although management of cardiac aging and heart diseases with non-pharmacological regimens such as life style and dietary modification benefits organismal health, the application of pharmacotherapies targeting autophagy remains dismal for the obesity-related cardiac aging and heart disease discussed here in this mini-review [128]. A better understanding of the mechanisms involved in obesity-induced heart aging should help to guide the drug development for these metabolic anomalies.

Transparency document

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

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Conflict of interest

The authors declare that they have no conflicts of interest with the contents of this article.

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