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Review

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Cardioprotective Effects of Adiponectin-Stimulated Autophagy

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ABSTRACT

Cardiovascular diseases (CVDs), including heart failure, pose a significant economic and health burden worldwide. Current treatment strategies for heart failure are greatly limited, in that they mainly mitigate symptoms or delay further progression. In contrast, therapies aimed at proactively preventing the onset of heart failure could greatly improve outcomes. Adiponectin is an adipocyte-derived hormone that confers an array of cardioprotective effects. It exerts anti-inflammatory effects, improves metabolic function, mitigates endothelial cell dysfunction, and reduce cardiomyocyte cell death. Furthermore, it has gained increasing attention for its ability to activate autophagy, a conserved cellular pathway that facilitates the degradation and recycling of cell components. The disruption of autophagy has been linked to CVDs including heart failure. Additionally, growing evidence also points to specific forms of autophagy, namely mitophagy and lipophagy, as crucial adaptive responses in protection against CVDs. The protective effects of adiponectin, autophagy, mitophagy, and lipophagy against CVDs along with potential therapeutic implications will be discussed.

Keywords: Adiponectin; Autophagy; Mitophagy; Lipophagy; Cardiovascular diseases

INTRODUCTION

Adiponectin, a hormone derived from adipocytes, bestows a variety of protective benefits for the heart. As a result, it has been established as a potentially important therapeutic target. To fully exploit the beneficial physiological effects of adiponectin it is important to fully understand its mechanisms of action. Previous work has demonstrated mechanisms such as anti-inflammatory effects, improved metabolic function, mitigated endothelial cell dysfunction, and reduced cardiomyocyte cell death.[1-5] Moreover, we and others have demonstrated its capacity to trigger autophagy, a fundamental cellular mechanism that aids in the breakdown and renewal of cellular components. Importantly, mounting evidence highlights that autophagy is a pivotal adaptive reaction guarding against heart failure, although excess or prolonged autophagy can be detrimental.[6,7] In this article the protective effects of adiponectin in the heart and mechanistic role of autophagy (particularly mitophagy and lipophagy) will be reviewed.

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Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author Contributions

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PHYSIOLOGICAL ROLE OF ADIPONECTIN AND AUTOPHAGY

Adiponectin is a hormone derived from adipocytes (adipokine) that is present in high concentrations in physiological settings ranging from 3–30 μg/mL of plasma. Since its initial characterization in adipocytes in 1995, adiponectin has gained increasingly more attention for its therapeutic potential.[8] One of the most architecturally complex adipokines, existing as trimers, hexamers, or high molecular weight oligomers, adiponectin can exert paracrine effects on target tissues such as the liver, heart, pancreas, kidney, and muscle. Its beneficial effects are partly attributed to its ability to activate AMP-activated protein kinase (AMPK) and mitigate cell death and inflammation, which have widespread implications for pathological conditions such as cardiovascular diseases (CVDs), atherosclerosis, obesity, and diabetes (**Fig. 1**). More recently, emerging evidence suggests that the protective effects of adiponectin can also be attributed to its ability to regulate autophagy.[9]

Autophagy is an intracellular catabolic process that mediates the clearance and recycling of damaged proteins or organelles through lysosomal degradation. Conserved across different cells and tissues, autophagy is especially important for the maintenance of cellular homeostasis in long-lived and postmitotic cells such as cardiomyocytes. Autophagy can be categorized into 3 major sub-classes: chaperone-mediated autophagy, microautophagy, and macroautophagy.[10] All 3 forms of autophagy result in lysosomal cargo degradation, but the mechanisms by which the cargo is delivered differ. Macroautophagy, the subtype primarily discussed herein, is hereafter referred to as autophagy. In contrast to general

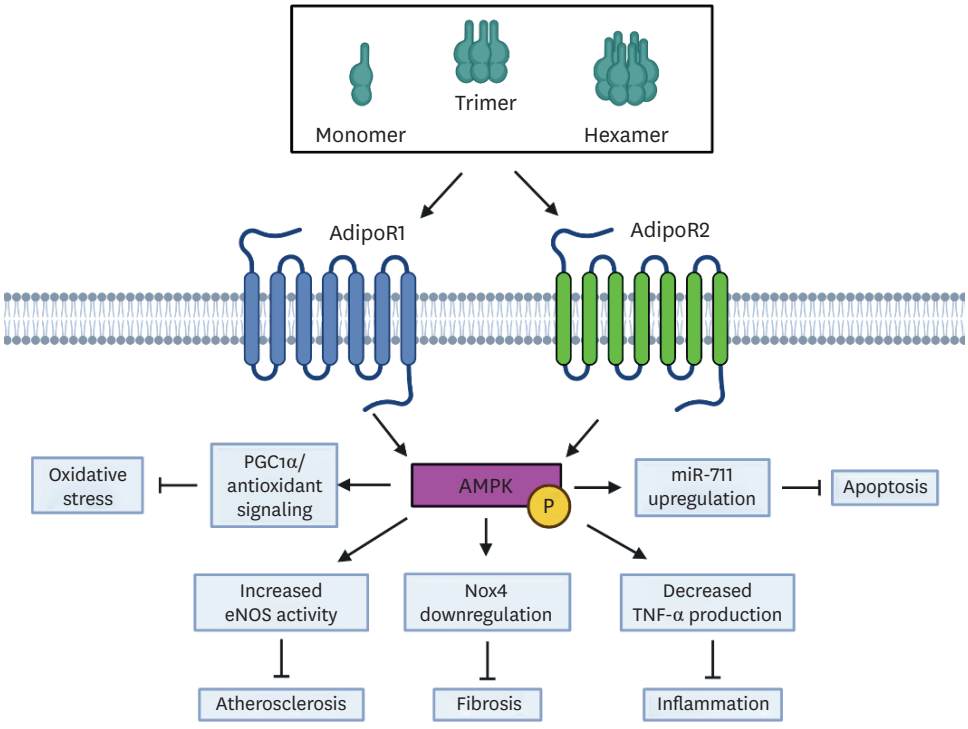

Fig. 1. Adiponectin confers cardioprotection via AdipoR1/2-AMPK signaling.
Adiponectin, existing in a monomeric, trimeric, or oligomeric form binds to AdipoR1/2. Upon binding, AMPK is activated, which dampens oxidative stress, atherosclerosis, apoptosis, fibrosis, and inflammation.
AdipoR1/2, adiponectin receptors 1 or 2; AMPK, AMP-activated protein kinase; PGC1α, peroxisome proliferator-activated receptor-γ coactivator 1α; eNOS, endothelial nitric oxide synthase.

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autophagy, which involves the bulk degradation of cytoplasmic content, selective autophagy relies on specific receptors that recognize and tag the targeted cargo for engulfment by autophagosomes. Examples of selective autophagy include mitophagy, which targets damaged mitochondria, and lipophagy, which targets lipid droplets. Tightly regulated at both the transcriptional and translational levels, autophagy can be initiated via the unc-51 like autophagy activating kinase 1 (ULK1) complex that is canonically activated upon nutrient starvation.[10,11] Subsequently, ULK1 activates the class III phosphoinositide 3-kinase (PI3K) complex, resulting in the recruitment of key autophagy proteins that mediate phagophore formation and expansion.[11] Following engulfment of autophagic cargo, autophagosomes are tethered to lysosomes via Soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) proteins, Rab7, and other GTPases that facilitate autophagosome-lysosome fusion.[12] Cytosolic cargo is ultimately degraded in the newly formed autolysosomes, and the resulting breakdown constituents such as amino acids are recycled for use as summarized in **Fig. 2**.[13] The importance of autophagy in the heart, which has an extremely limited regenerative capacity, making it susceptible to even minute disturbances in cellular homeostasis, cannot be understated.[14] The pleiotropic cardioprotective effects of autophagy, in part attributed to its ability to maintain energy metabolism, facilitate clearance of dysfunction mitochondria, and regulate proteostasis, are discussed below.

Mitophagy is a selective autophagy subtype that mediates the degradation of damaged or dysfunctional mitochondria and is critical for maintaining mitochondrial quality control.

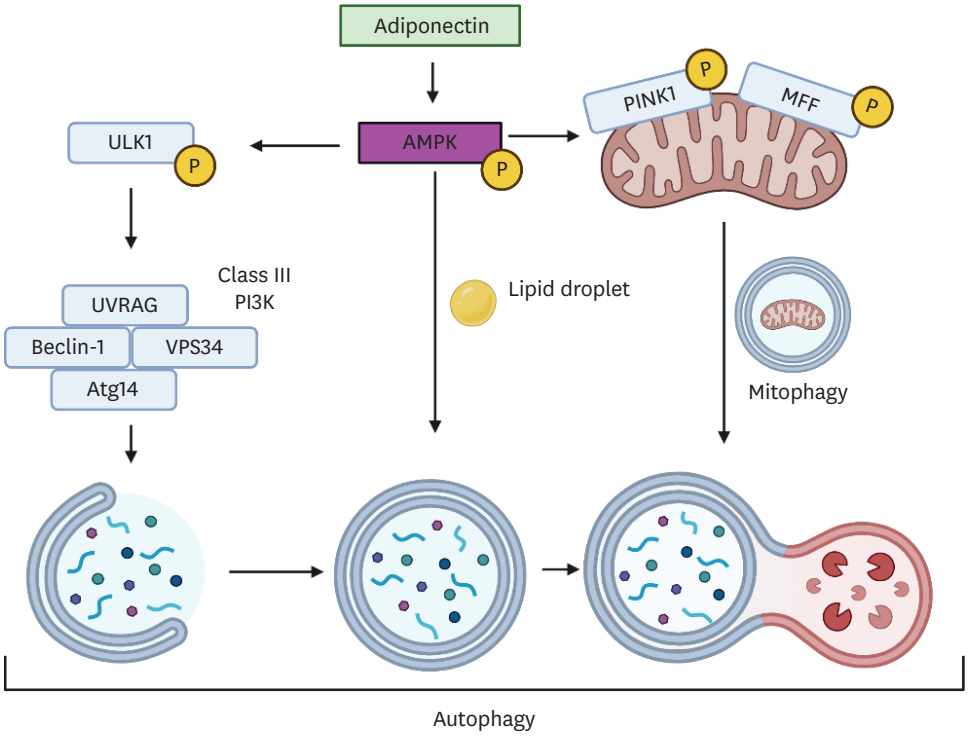

Fig. 2. Mechanisms via which adiponectin stimulates autophagy.
Adiponectin mediates activation of AMPK. AMPK phosphorylates ULK1 resulting in subsequent activation of the class III PI3K complex and initiating the formation of phagophore for autophagy. AMPK phosphorylates PINK1 and MFF to promote recruitment of autophagic machinery to mitochondria and activation of mitophagy. AMPK signaling also plays a role in mediating the autophagic degradation of lipids in a process termed lipophagy.
AMPK, AMP-activated protein kinase; PI3K, phosphoinositide 3-kinase; PINK1, PTEN induced kinase 1; MFF, mitochondrial fission factor.

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Maintenance of mitochondrial health is important in the heart because mitochondria comprise up to 40% of the volume of cardiomyocytes yet are responsible for up to 95% of energy for cardiac function.[15] In the aging heart, mitochondria are enlarged with loss of mitochondrial structure, and elimination via mitophagy becomes especially important to cell function.[16] This becomes increasingly important for cardiomyocytes, which have a relatively low turnover rate. Thus, mitochondrial disturbances must be dealt with quickly.

The PTEN induced kinase 1 (PINK1)/Parkin-dependent form of mitophagy is the most studied. In that pathway, PINK1 is normally imported into the mitochondria for proteolytic degradation by PARL.[17] Upon damage to the mitochondria and loss of membrane potential, PINK1 stability increases, and it accumulates on the outer mitochondrial membrane.[17] This accumulation of PINK1 on mitochondria allows for the recruitment of the E3 ligase Parkin, which is normally localized to the cytosol.[18] Parkin ubiquitinates several proteins such as MFN1, MFN2, and MIRO, and these ubiquitinated substrates serve as recognition sites for cargo receptors such as SQSTM1/p62 to facilitate autophagy.

Mitophagy can also occur via a receptor-mediated pathway. Three mitophagy receptors have been identified: Bcl-2 interacting protein 3 (BNIP3), NIX, and FUN14 domain containing 1 (FUNDC1), all of which reside at the outer mitochondrial membrane.[19] They primarily facilitate mitophagy through their LC3-interacting region (LIR) motif containing the tetrapeptide sequence W/F/YxxL/I.[20] The role of mitophagy in the context of CVDs will be further explored in a subsequent section. The role of adiponectin in mediating autophagy, lipophagy, and mitophagy are summarized in **Fig. 2**.

DYSREGULATION OF AUTOPHAGY IN HEART FAILURE

Heart failure as a result of adverse cardiac remodelling can be traced back to cellular and molecular changes. This leads to ventricular dysfunction, culminating in heart failure. Examples of cellular/molecular changes that contribute to the development of heart failure include loss of proteostasis, inflammation, and cell death.[21,22] Since autophagy can supress these adverse changes, it is not surprising that dysregulation of autophagy has been implicated in the development of heart failure.

The loss of proteostasis, which is the homeostasis between protein trafficking, folding, and clearance, is a key contributor. When the loss of proteostasis occurs due to the accumulation of misfolded proteins, a phenomenon called endoplasmic reticulum (ER) stress can occur. Left unchecked, ER stress can contribute to the progression towards heart failure. For example, signs of ER stress, which include increased GRP78 and XBP1, were observed in patients with heart failure.[23] The Lys-Asp-Glu-Leu (KDEL) receptor serves as a recognition site for ER chaperones to facilitate quality control. Expressing a mutant form of KDEL led to protein aggregation and the development of dilated cardiomyopathy.[24] Autophagy can protect against heart failure by supressing ER stress. In fact, autophagy can be activated in response to ER stress via the IRE-1-JNK/p38 or PERK-eIF2α-ATF4 pathway. Activation of these pathways induces autophagy by upregulating beclin-1 and several autophagy genes.[25] Therefore, autophagy dysregulation can result in unresolved ER stress that contributes to heart failure progression.

Inflammation is a hallmark of CVDs, with anti-inflammatory therapeutics having demonstrated some success.[26] Moreover, inflammation is intricately linked to the process

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of autophagy—both of which contribute to the pathogenesis of heart failure.[27] For instance, Saitoh et al.[28] showed that macrophages from Atg16l1 knockout (KO) mice exhibit elevated interleukin (IL)-1β upon lipopolysaccharide, which was attributed to increased activation of caspase 1.[28] Additionally, autophagy reduces nuclear factor-kappa B levels through degradation of BCL10. Similarly, mitophagy can also regulate inflammation. Activation of PINK1/Parkin-dependent mitophagy helps maintain mitochondrial homeostasis including ATP and membrane potential. This helps in preventing release of excess reactive oxygen species (ROS) or damage-associated molecular patterns (including mitochondrial DNA) into the cytosol, thus mitigating downstream inflammation.[29] These studies indicate that autophagy plays an important role in supressing inflammation, such as that observed in the failing heart. Consequently, a dysregulation of autophagy may contribute to the development of heart failure.

DYSREGULATION OF ADIPONECTIN AND AUTOPHAGY IN CVD MODELS

There is an abundance of evidence pointing to the protective role of adiponectin against metabolic diseases.[30-32] Given the close relationship between metabolic dysfunction and risk for CVDs, it is not surprising that adiponectin also demonstrates therapeutic effects against CVDs. For example, adiponectin protects the heart from ischemia-reperfusion (I/R) injury through inhibition of inducible nitric oxide synthase and attenuated ROS levels, in an AMPK-independent manner.[33] Endothelial cells play an important role in paracrine signaling within the heart to regulate the vascular tone and inflammation. Endothelial dysfunction and elevated Ras activity are ways in which atherosclerosis can develop or become exacerbated.[34] Endothelial nitric oxide synthase (eNOS) activity is critical in regulating vasoconstriction and vasodilation.[34] There is increasing evidence that adiponectin plays an important role in endothelial function. For example, Chen et al.[35] show that adiponectin increased levels of vasodilator nitric oxide in vascular endothelial cells. Similarly, adiponectin-deficient mice exhibit impaired vasodilation and eNOS.[36] Tan et al.[37] corroborated these findings where they showed diabetic patients with hypoadiponectemia have lower vasodilation response. Thus, decreased adiponectin may underly endothelial dysfunction, metabolic dysfunction, and subsequent CVD. Indeed, lower adiponectin concentrations are associated with metabolic risk factors for atherosclerosis and CVDs.[38] Adiponectin can regulate eNOS activity in different ways. Adiponectin signaling increased eNOS activity through phosphorylation at Ser1179 in a PI3K dependent manner.[35] This was also confirmed where adiponectin treatment of human umbilical vein endothelial cell increased eNOS at the mRNA and protein level.[3] Adiponectin regulates eNOS through different mechanisms which promote vasodilation effects. Furthermore, perivascular adipose tissue-derived adiponectin has been shown to protect mice against the development of atherosclerosis by activating macrophage autophagy via suppression of the Akt/FOXO3a pathway.[39]

Patients with hypertension have lower adiponectin levels, the latter being inversely correlated with risk for hypertension.[40] Interestingly, supplementation of adiponectin in obese mice was sufficient to decrease blood pressure.[36] Ang-II-induced hypertension decreased adiponectin in vascular cells.[41] Conversely, angiotensin-converting enzyme inhibitors (ACEi) or Ang-II inhibition were correlated with higher adiponectin levels in pathological states.[42,43] ACEis are among the first-line treatment strategies for heart failure and the evidence provided suggests that the cardioprotective effects of ACEi could be attributed to adiponectin-like effects.

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Together, this demonstrates that adiponectin can regulate signaling pathways to promote vasodilation or activate autophagy to protect against atherosclerosis and hypertension.

Pressure overload is a commonly used preclinical model for heart failure. In principle, it causes mechanical load, resulting in left ventricular hypertrophy that is a widely known precursor for heart failure.[44] Shibata et al.[45] found that adiponectin deficiency exacerbated cardiac hypertrophy in a model of pressure overload whilst adiponectin activated AMPK signaling, and in vitro, it reduced hypertrophic signaling.[45] A recent study showed that adiponectin can activate MEF2 via the p38 pathway in cardiomyocytes, which has implications for cardiac hypertrophy. Following pressure overload, mice exhibit increased cardiac hypertrophy and dysfunction. This cardiac dysfunction was accompanied with an increase in hypertrophic genes in wild-type mice but attenuated in mice lacking adiponectin. Pressure overload-induced activation of hypertrophic MEF2 was found to be dependent upon adiponectin signaling via the p38 pathway.[46] Autophagy in late stages of pressure overload were found to correlate with the magnitude of hypertrophic growth and rate of transition to heart failure.[47] For example, cardiomyocytes overexpressing Beclin 1 display enhanced autophagic response following biomechanical stress and this resulted in pathological remodeling processes.[47] In contrast, mice heterozygous for Beclin 1 had blunted autophagic responses to stress and adverse cardiac remodeling was attenuated.[47] Together, this shows that prolonged stress-induced autophagy is maladaptive. In contrast, autophagy deficiency accomplished via inactivation of Atg5 gene deteriorated cardiac function in both basal and disease states.[48] Similarly, cardiac-specific deletion of Atg5 led to cardiac hypertrophy and contractile dysfunction. Finally, adiponectin KO mice with impaired autophagy exhibit worse cardiac function in a model of pressure overload.[49] Overall, we conclude that basal autophagy in the heart is essential in the maintenance of cardiac homeostasis. In models of pressure overload, adiponectin-mediated autophagy is protective against pressure overload.

Myocardial infarction (MI), commonly known as a heart attack, occurs when there is a blockage of blood flow in the heart. It can cause permanent damage to the heart and increase the risk for subsequent MI occurrences.[50,51] Furthermore, patients who suffer an MI are at heightened risk for heart failure, with a marked 5-year mortality of up to 50%.[51] The treatment strategy for MI is timely reperfusion to salvage viable tissue within the ischemic heart. Unfortunately, reperfusion following MI causes a paradoxical dysfunction of cardiomyocytes in a process termed I/R injury. Healthy adults with lower levels of adiponectin have an elevated risk for MIs and worse outcomes.[52] For example, I/R injury caused cardiac damage that was exacerbated in adiponectin KO mice.[53] In the same study, overexpression of adiponectin, or exogenous adiponectin administration stimulated AMPK and cyclooxygenase-2 (COX2), which inhibited apoptosis, inflammation, reduced infarct size, and improved cardiac function. Additionally, adiponectin activates the AMPK-Akt-eNOS-NO and AMPK-COX2 signaling pathways to inhibit oxidative stress.[54] It is important to note that high adiponectin levels are not always cardioprotective. For instance, a clinical study found that high adiponectin levels are correlated with adverse cardiovascular outcomes such as heart failure in patients with stable ischemic heart disease.[55] Although autophagy is generally regarded as protective during ischemia, the precise role of autophagy during the reperfusion phase is highly context dependent. For example, autophagy activated by the AMPK pathway was protective and loss of this was detrimental for myocardial injury.[56] Furthermore, the AMPK activator PT1 was found to be effective at mitigating myocardial cell death caused by I/R. PT1 was found to activate autophagy and reduce infarct size.[57] In contrast, autophagy can be activated in an AMPK-independent manner. The autophagy regulator Beclin 1 is

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upregulated during the reperfusion phase by ROS.[56] Reduced Beclin 1 in a mouse model of I/R caused a marked reduction in autophagy and reperfusion injury.[56] However, a global reduction in autophagy mediated through KO of Atg7 yielded adverse cardiac outcomes following I/R injury.[58] Collectively, this suggests that adiponectin and autophagy largely exert a cardioprotective effect, with certain caveats. Namely, AMPK-mediated autophagy is protective, but Beclin1-dependent autophagy is detrimental during the reperfusion phase of I/R injury.

Cardiomyocytes strictly regulate lipid metabolism to avoid lipotoxicity, with excess fatty acids esterified and stored as triglycerides in cytosolic lipid droplets. During ischemia, cardiomyocytes undergo metabolic changes, including increased reliance on anaerobic glycolysis and decreased fatty acid oxidation, leading to the accumulation of lipid droplets. Interestingly, enhancing cardiac triglyceride metabolism improves recovery from ischemic stress following I/R.[59] Recent evidence highlights a role for adiponectin signaling in promoting hepatic lipid droplet catabolism via lipophagy, the autophagic degradation of lipid droplets.[60,61] Yet, whether adiponectin-mediated autophagy activation mitigates lipid droplet buildup in cardiomyocytes through a similar mechanism is unknown. Understanding the mechanisms underlying lipid droplet metabolism and lipophagy in heart failure could offer novel therapeutic targets for mitigating the progression of this condition.

DYSREGULATION OF MITOPHAGY IN CVDs

BNIP3 and BNIP3L/NIX are involved in regulating apoptosis or necrosis via Bcl-2 interactions.[62] BNIP3L/NIX and BNIP3 are upregulated in response to hypoxia through transcriptional signaling from hypoxia inducible factor or FOXO3.[62] Furthermore, BNIP3 phosphorylation at Ser17 and Ser24 promote LC3 binding and mitophagy.[62] There is also some evidence implicating Rheb interactions and BNIP3L to promote mitophagy in oxidative cells.[63]
Like other autophagy receptors, FUNDC1 contains a LIR motif and is upregulated by hypoxia. FUNDC1 activity is controlled by phosphorylation.[64] Dephosphorylation at Ser13 and Tyr18 mediated by PGAM5 occurs in response to hypoxia or mitochondrial membrane depolarization.[64] The dephosphorylated form binds more strongly to LC3, thus promoting mitophagy.[64] Under physiological conditions, FUNDC1 is phosphorylated by Src kinase and CK2—2 highly constitutively active kinases.[64] This ensures a strong inhibition of FUNDC1-dependent mitophagy.

Alternative mitophagy occurs through a distinct pathway that is largely independent of the canonical autophagy machinery. It occurs through a pathway dependent on Ulk1/Drp1/Rab9.[65] This was demonstrated whereby a Rab9 S179A mutant impaired alternative mitophagy and subsequently led to adverse effects in a model of ischemic injury.[65,66] This phenomenon did not alter conventional autophagy. The timing of alternative mitophagy is also distinct, in that it often occurs after conventional mitophagy or autophagy during heart failure. For example, in an animal model of obesity-associated cardiomyopathy, mitophagy was upregulated 3 weeks after high-fat diet (HFD) feeding and persisted through to week 24.[67] It was found that in the chronic phase, week 20 and later, the predominant form of mitophagy was the alternative form.[67] This form of mitophagy was found to be protective against obesity-induced cardiomyopathy through maintaining mitochondrial quality control. The protective effects of alternative mitophagy are further exemplified in a model of pressure overload. Loss of alternative mitophagy via KO of Ulk1 exaggerated cardiac injury in a model of pressure overload

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without compromising conventional autophagy.[68] Thus, alternative mitophagy mediated via Ulk1/Drp1/Rab9 provides cardioprotection in pathological conditions, in a conventional autophagy-independent manner.[68]

Mitophagy also plays an important role in myocardial remodeling after MI. Loss of BNIP3 reduced apoptosis 2 days after MI. Furthermore, 3 weeks post MI, BNIP$^{-/-}$ mice have improved cardiac function. Increased BNIP3 expression in the heart elevated apoptosis both at basal and MI conditions, resulting in cardiac dysfunction. This study demonstrated that BNIP3 mediates adverse cardiac remodeling in the infarcted heart.[69] Similarly, Nix is upregulated following pressure overload and has been associated with cardiac hypertrophy. Nix expression levels were positively correlated with hypertrophy leading to cardiomyocyte apoptosis, and cardiac dysfunction. In contrast, Nix ablation reduced apoptosis and improved cardiac function. Mice with cardiac-specific KO of Nix exhibit less adverse cardiac remodeling following transverse aortic constriction (TAC). These findings suggest Nix induces cardiomyocyte apoptosis and adverse remodeling in a model of hypertrophy.[70] On the other hand, mitophagy mediated by FUNDC1 is cardioprotective against I/R injury. Using a FUNDC1 KO mouse model and biochemical approach blocking FUNDC1-LC3 interaction, it was demonstrated that mitophagy is upregulated by hypoxia or I/R and this process was important for mitochondrial quality control in vivo. Furthermore, hypoxic preconditioning induced FUDNC1-dependent mitophagy in platelets, and reduced cardiac I/R injury, indicating its cardioprotective potential.[71] Likewise, Parkin-dependent mitophagy has also been shown to be protective in the cardiac setting. For instance, impairment of mitophagy via p53 led to mitochondrial dysfunction and heart failure in mice. p53 accomplishes this through binding to Parkin and supressing its translocation to mitochondria. Mice deficient in p53 exhibit improved mitochondrial health and cardiac function. Thus, inhibition of p53 could be harnessed to activate mitophagy and improve heart failure.[72] In Parkin deficient mice, hearts had smaller mitochondria, and disorganized networks though cardiac function and mitochondrial function remained largely unchanged. However, these mice had an increased susceptibility to MI which was attributed to reduced mitophagy and accumulation of dysfunctional mitochondria. Furthermore, overexpression of Parkin in cardiomyocytes protected against hypoxia-induced cell death. This suggests Parkin plays an important role mediating adaptive stress responses in the heart via mitophagy.[73] Statins are a class of drugs that are routinely recommended as a preventative measure against heart failure in patients with MI or acute coronary syndrome.[74] It is now known that statins confer cardioprotection partly through upregulation of Parkin-dependent mitophagy.[75] Therefore, while mitophagy can generally be regarded as beneficial in the heart, the specific pathway through which it occurs may dictate its ultimate effect. Specifically, the evidence suggests mitophagy via the FUNDC1, Parkin, or alternative pathway are beneficial whereas the BNIP3 and NIX pathway are maladaptive (**Fig. 3**).

ADIPONECTIN AND AUTOPHAGY AS THERAPEUTIC TARGET FOR HEART FAILURE

Having discussed the cardioprotective effects of adiponectin and autophagy individually, the evidence implicating adiponectin's ability to stimulate adaptive autophagy and implications in various models of heart failure will be discussed. Autophagy is a critical regulator of cardiac hypertrophy. Depending on the context, autophagy can be adaptive or maladaptive. Dämmrich and Pfeifer[76] reported a reduced autophagic response in rats following aortic

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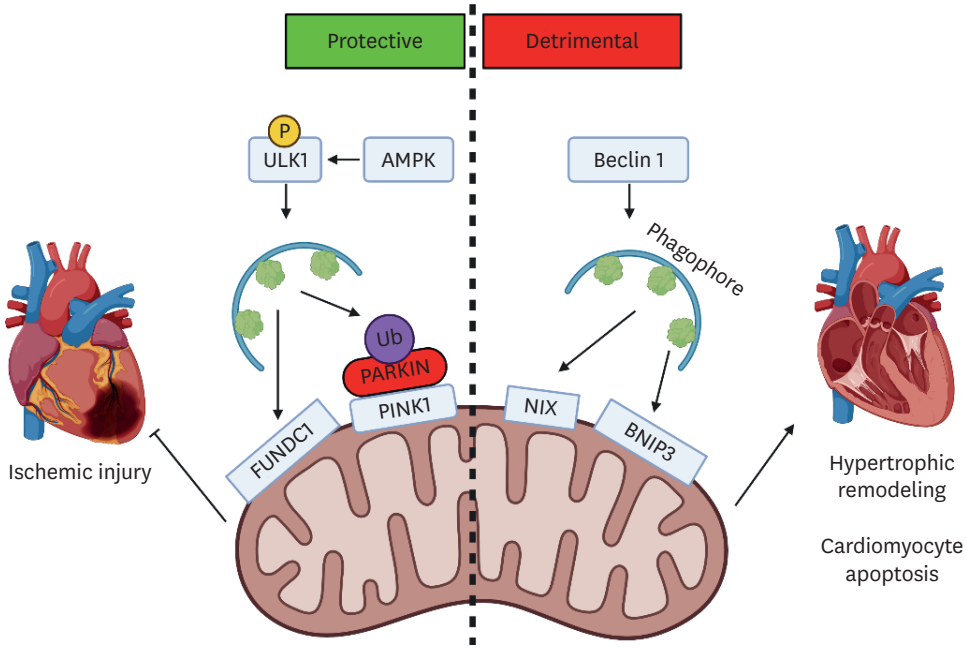

Fig. 3. Distinct roles of mitophagy in the cardiovascular setting.
AMPK signaling leads to phosphorylation and activation of ULK1 to facilitate protective autophagy. Mitophagy occurring through PINK1/Parkin or FUNDC1 is known to be protective against ischemic heart diseases. Upregulation of autophagy mediated through Beclin 1 is detrimental. Activation of mitophagy via NIX or BNIP3 is detrimental.
AMPK, AMP-activated protein kinase; ULK1, unc-51 like autophagy activating kinase 1; PINK1, PTEN induced kinase 1; FUNDC1, FUN14 domain containing 1; BNIP3, Bcl-2 interacting protein 3.

constriction. Deficiency in adiponectin enhanced HFD induced cardiac hypertrophy and cardiac dysfunction, potentially due to reduced autophagy by AMPK.[76] Adiponectin deficiency also promoted Ang-II induced inflammation and fibrosis, which was associated with reduced macrophage autophagy in the heart.[77] Adiponectin is anti-inflammatory in that it can elevate the production of anti-inflammatory IL-10 in human monocytes, macrophages, and dendritic cells.[78] Furthermore, it is known that AMPK is a crucial regulator of IL-10 signaling.[79] It has been shown that IL-10 signaling was protective in reducing pathological cardiac hypertrophy.[80] Using a tumor necrosis factor-induced and TAC-induced cardiac hypertrophy model, Stafford et al.[80] showed that loss of IL-10 receptor resulted in significant increase in cardiac hypertrophy and fibrosis. The anti-inflammatory effects of adiponectin are further illustrated by Cho et al.[81] where the use of adiponectin receptor agonist, ALY688, conferred cardioprotective effects in a preclinical mouse model of heart failure. At the gene expression level, ALY688 was able to supress pro-inflammatory cytokines and pro-fibrotic genes.[81] A separate study demonstrated ALY688 could activate adiponectin signaling validating its adiponectin-mimetic effects.[82] Therefore, the cardioprotective effects of adiponectin can also be attributed to its ability to exert anti-inflammatory effects, possibly via autophagy.

Beta-adrenergic receptor autoantibodies (Beta-AA) have been shown to induce heart failure in preclinical models and are elevated in patients with heart failure. The binding of Beta-AA to the receptors are known to cause a prolonged activation of the receptors which ultimately contribute to contractile dysfunction.[83] Furthermore, it is known that Beta-AA can decrease myocardial autophagic flux leading to cell death and cardiac dysfunction. Additionally, Beta-AA also decreased AMPK phosphorylation and adiponectin deficiency aggravated this effect. Adiponectin administration restored AMPK activity, improved autophagic flux,

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and mitigated Beta-AA-induced cardiac dysfunction.[84] These findings are consistent with humans, where adiponectin levels are inversely correlated with adverse cardiovascular events in aged populations. Finally, while hypertrophic hearts shift metabolism away from fatty acid utilization toward glucose utilization for energy production, adiponectin improves cardiac metabolism by regulating both glucose and lipid metabolism.[85] In obese mice overexpressing adiponectin receptor 1, the reduced lipid accumulation and hypertrophy observed in the heart were attributed to increased autophagic gene expression.[86] Collectively, these studies show that autophagy is an important cell process through which adiponectin positively remodels the cardiovascular system.

CONCLUSIONS

Adiponectin plays physiological role and has immense therapeutic potential due to its ability to mediate paracrine effect on various target. Its benefits are attributed to its ability to alleviate cell death and inflammation which have implications for conditions such as metabolic and CVDs. Increasing evidence has pointed towards autophagy as a way through which adiponectin exerts its protective effects. Autophagy is dysregulated in heart failure which may explain the loss of proteostasis, cell death, and inflammation. A low level or complete loss of adiponectin is correlated with worse outcomes in various preclinical models of CVDs including atherosclerosis, hypertension, pressure overload, and ischemia reperfusion injury. Adiponectin promotes endothelial function by promoting vasodilation or autophagy to protect against atherosclerosis and hypertension. ACEis are cardioprotective and is likely in part due to adiponectin-mediated effects. Autophagy in pressure overload and ischemia reperfusion injury is largely protective for homeostasis and mitigates adverse remodeling. The beneficial effects of adiponectin are largely attributed to AMPK-dependent signaling. Lipophagy, the selective autophagy of lipid droplets, has been shown to be regulated by adiponectin signaling. Lipotoxicity in the stress myocardium may be averted through adiponectin stimulated autophagy and lipophagy, however the mechanisms underlying this in the cardiac setting necessitates further investigations. Mitophagy occurring via FUNDC1 or PINK1 pathway are largely protective, however BNIP3 or Nix dependent mitophagy are detrimental in the cardiac setting. This contrasting effect could be due to adiponectin differentially altering certain pathways over another, though this remains to be fully characterized. AMPK signaling promotes PINK1 mitophagy, yet the effect of adiponectin on other pathways remains to be fully characterized. Adiponectin deficiency was associated with reduced autophagy and increased propensity toward inflammation and fibrosis in a model of hypertension. Adiponectin, working through AMPK signaling promotes anti-inflammation which is a widely known to play protective effects in heart. The adiponectin receptor agonist, ALY688, demonstrated cardioprotective effects in a preclinical model of heart failure by supressing inflammation and fibrosis, likely in part through activation of autophagy. Adiponectin also improves metabolism which can contribute to reducing lipotoxicity seen in pathological hearts. Overall, adiponectin is protective against various CVDs working through different mechanisms including autophagy.

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