ESC European Society of Cardiology

European Heart Journal (2020) **41**, 3856–3861
doi:10.1093/eurheartj/ehaa360

SPECIAL ARTICLE
Heart failure

Longevity genes, cardiac ageing, and the pathogenesis of cardiomyopathy: implications for understanding the effects of current and future treatments for heart failure

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Received 7 March 2020; revised 26 March 2020; editorial decision 16 April 2020; accepted 17 April 2020; online publish-ahead-of-print 27 May 2020

The two primary molecular regulators of lifespan are sirtuin-1 (SIRT1) and mammalian target of rapamycin complex 1 (mTORC1). Each plays a central role in two highly interconnected pathways that modulate the balance between cellular growth and survival. The activation of SIRT1 [along with peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α) and adenosine monophosphate-activated protein kinase (AMPK)] and the suppression of mTORC1 (along with its upstream regulator, Akt) act to prolong organismal longevity and retard cardiac ageing. Both activation of SIRT1/PGC-1α and inhibition of mTORC1 shifts the balance of cellular priorities so as to promote cardiomyocyte survival over growth, leading to cardioprotective effects in experimental models. These benefits may be related to direct actions to modulate oxidative stress, organellar function, proinflammatory pathways, and maladaptive hypertrophy. In addition, a primary shared benefit of both SIRT1/PGC-1α/AMPK activation and Akt/mTORC1 inhibition is the enhancement of autophagy, a lysosome-dependent degradative pathway, which clears the cytosol of dysfunctional organelles and misfolded proteins that drive the ageing process by increasing oxidative and endoplasmic reticulum stress. Autophagy underlies the ability of SIRT1/PGC-1α/AMPK activation and Akt/mTORC1 suppression to extend lifespan, mitigate cardiac ageing, alleviate cellular stress, and ameliorate the development and progression of cardiomyopathy; silencing of autophagy genes abolishes these benefits. Loss of SIRT1/PGC-1α/AMPK function or hyperactivation of Akt/mTORC1 is a consistent feature of experimental cardiomyopathy, and reversal of these abnormalities mitigates the development of heart failure. Interestingly, most treatments that have been shown to be clinically effective in the treatment of chronic heart failure with a reduced ejection fraction have been reported experimentally to exert favourable effects to activate SIRT1/PGC-1α/AMPK and/or suppress Akt/mTORC1, and thereby, to promote autophagic flux. Therefore, the impairment of autophagy resulting from derangements in longevity gene signalling is likely to represent a seminal event in the evolution and progression of cardiomyopathy.

Keywords Heart failure • Sirtuin-1 • Akt/mTOR pathway • Adenosine monophophase-activated protein kinase • Cardiac ageing

The two primary molecular regulators of lifespan identified to date are sirtuin-1 (SIRT1) and mammalian target of rapamycin (mTOR).[1] Each gene represents the cornerstone of two interconnected pathways that regulate the balance between cellular growth and survival. When nutrients are plentiful, organisms prioritize the utilization of fuels to expand the cell mass, and mTOR signalling is central to this process. In contrast, when nutrients are in short supply, organisms minimize the utilization of anabolic pathways and adopt a safe and sheltered set of biological conditions that preserve the structural and functional integrity of existing cells; SIRT1 is critical to this response.

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SIRT1 and Akt/mTOR signalling in the regulation of organismal longevity, cardiac ageing, and cardiomyocyte survival

The counterbalancing effects of SIRT1 and mTOR control the set point between cellular growth and cellular homeostasis. The positioning of this set point is exquisitely sensitive to the environmental energy supply and the redox state.[2,3]

Role of SIRT1 in organismal longevity and cardiac ageing

SIRT1 is one of a family of redox-sensitive nicotinamide adenine dinucleotide-dependent deacetylases that catalyse the post-translational modification of hundreds of proteins that are involved in metabolism and cellular homeostasis. The yeast orthologue of SIRT1 is *Sir2* (silent information regulator 2). Overexpression of *Sir2* extends lifespan,[4] and the ability of caloric restriction to prolong survival in yeast is dependent on the action of *Sir2* to produce cytoprotective effects.[5] Interestingly, in mammals, the organ that is critically involved in the longevity effects of *Sir2* is the heart. The mammalian orthologue of *Sir2* plays an essential role in mediating cell survival in cardiac myocytes,[6] and mice that are deficient in *Sir2α* (the murine orthologue of *Sir2*) exhibit developmental abnormalities in the heart[7] and develop early-onset heart failure.[8,9]

The expression of SIRT1 in most organs diminishes following birth, but it normally persists at high levels in the healthy heart,[10] unless the myocardium exhibits the effects of ageing or shows evidence of a cardiomyopathic process.[11,12] Mild-to-moderate up-regulation of SIRT1 prevents ageing in the heart,[13] and SIRT1 has cardioprotective effects in a broad range of experimental models (*Figure 1*). Activation of SIRT1 activates antioxidant mechanisms and reduces oxidative stress, promotes mitochondrial health and biogenesis, and diminishes proinflammatory pathways in cardiomyocytes in order to promote cell survival.[14–16] SIRT1 also mediates the ability of redox modulators and inflammasome suppressors to attenuate cardiac hypertrophy and to reduce cell senescence and death following cardiac injury.[17,18] Cardiac-specific deletion of SIRT1 in mice augments mitochondrial production of reactive oxygen species, enhances oxidative and endoplasmic reticulum stress, and sensitizes the heart to pressure overload and ischaemia/reperfusion injury, leading to cardiac dysfunction and cardiomyopathy.[19–21] Conversely, SIRT1 enrichment or activation improves cardiac function and prevents adverse ventricular remodelling following experimental infarction[22,23]; mitigates cardiac injury and mitochondrial dysfunction produced by diverse cellular stresses[24–26]; and ameliorates fibrosis produced by pressure overload.[27] In experimental models of heart failure, activation of SIRT1 restores the functionality of sarco-endoplasmic reticulum Ca^{2+}-ATPase and improves cardiac function,[28,29] whereas suppression of SIRT1 decreases angiogenesis and leads to systolic and diastolic abnormalities.[19,21,30]

Many of the adaptive effects of SIRT1 signalling on organellar health and cellular stress are mediated or facilitated by its action to deacetylate peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α), a member of a family of transcription coactivators that play a central role in the regulation of cellular energy metabolism. Like SIRT1, PGC-1α exerts cardioprotective effects in numerous experimental models as a result of its actions to promote mitochondrial biogenesis and antioxidant mechanisms, while suppressing inflammation (*Figure 1*).[31–34] Loss of PGC-1α signalling is accompanied by an accelerated transition from hypertrophy to heart failure.[35] Cardiac-specific deletion of PGC-1α leads to impaired oxidative metabolism, increased oxidative stress and the development of dilated cardiomyopathy.[36,37] Interestingly, both cardiac ageing and heart failure are characterized by a decline in the expression and activity of PGC-1α,[37–40] and activation of PGC-1α leads to attenuation of the ageing process in the myocardium and amelioration of the development of heart failure.[41,42] PGC-1α hypomorphic mice show a vascular senescence phenotype that is associated with increased reactive oxygen species, mitochondrial abnormalities, and reduced telomerase activity.[43] Suppression of PGC-1α recapitulates age-related changes in mitochondrial gene expression, whereas up-regulation prevents senescence-related changes in the myocardium.[41]

These experimental observations supporting an important cardioprotective effect of SIRT1/PGC-1α signalling are consistent with studies showing a linkage between SIRT1/PGC-1α activity and cardiac disorders (including heart failure) in the clinical setting. Polymorphisms of SIRT1 in humans are associated with cardiac developmental abnormalities[44] and an increased predisposition to cardiac injury[45,46] and cardiac hypoperfusion syndromes.[47] Conversely, gain of function polymorphisms in the gene for PGC-1α have been linked with longer lifespans in clinical cohorts.[48] Down-regulation of SIRT1 is accompanied by increase in oxidative stress and inflammatory signalling in human cardiomyocytes.[11] Circulating levels of SIRT1 are inversely related to levels of proinflammatory cytokines in patients with coronary artery disease; low SIRT1 levels are accompanied by increased telomere attrition.[49] SIRT1 expression is decreased in peripheral blood monocytes in patients with Type 2 diabetes[50] and in patients with obesity with increased epicardial adipose tissue volume.[51] The expression of SIRT1 is suppressed both in peripheral

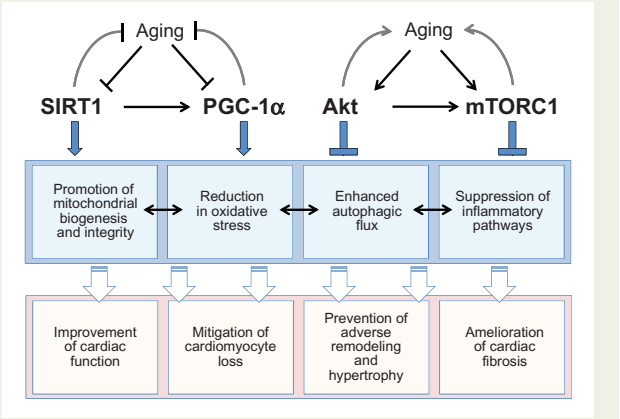


Figure 1 Effects of nutrient sensor signalling on the cellular mechanisms that underlie cardioprotection. Cellular mechanisms are shown in blue, and cardiac responses are shown in red. Akt, protein kinase B; mTORC1, mammalian target of rapamycin complex 1; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator-1alpha; SIRT1, sirtuin-1.

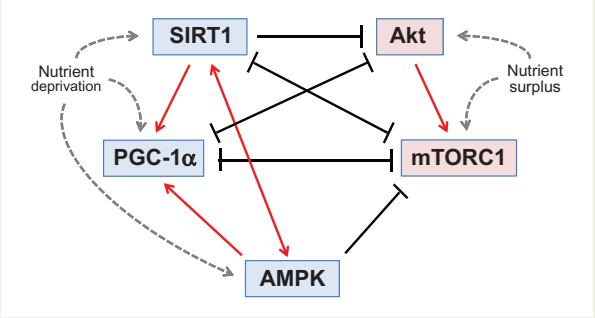


Figure 2 Mutual enhancement and antagonism of nutrient sensor signalling in the regulation of autophagic flux in cardiomyocytes. Nutrient deprivation sensors that promote autophagic flux are shown in blue, whereas the nutrient surplus sensors that suppress autophagy are shown in red. Akt, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; mTORC1, mammalian target of rapamycin complex 1; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator-1 alpha; SIRT1, sirtuin-1.

leucocytes and cardiomyocytes of patients with chronic cardiomyopathy.[52,53] Similarly, the expression of PGC-1α is depressed in the myocardium of patients with heart failure and a reduced ejection fraction[54–56] and is accompanied by defective mitochondrial replication and antioxidant defence mechanisms.[57]

Role of Akt/mTOR in organismal longevity and cardiac ageing

Both Akt and mTOR are serine/threonine protein kinases that function as critical promoters of cell growth and proliferation. mTOR exists in two complexes, mTOR complex 1 (mTORC1) and mTOR complex 2, and Akt potentiates the activation of mTORC1, which is preferentially inhibited by rapamycin.[1] Akt/mTORC1 signalling influences hundreds of downstream effectors that promote anabolic pathways, drives mitochondrial production of reactive oxygen species to facilitate cellular replication and innate immunity, and enhances the expression of the senescence-associated secretory phenotype that is essential to the cellular disposal required for effective organ growth.[58] Inhibition of mTOR redirects the priorities of the cell away from growth towards homeostasis and survival. mTOR suppression in yeast extends lifespan and is critical to the ability of caloric restriction to prolong survival in model organisms[59–61]; interestingly, the effect of mTOR on longevity in yeast is independent of the effects of *Sir2*. Mice with genetically-driven hypomorphic mTOR expression have an increased lifespan, an effect that is mimicked when mTOR activity is suppressed by rapamycin.[62]

The action of mTOR activity to promote anabolic pathways is required for cardiomyocyte replication during foetal development and adaptive hypertrophy during pressure overload,[63] but it contributes to maladaptive cardiac hypertrophy when hearts are stressed or injured in adulthood.[64] Specifically, complete cardiac-specific deletion of mTOR during embryonic development promotes lethality[63] and undermines the ability of the heart to tolerate states of rapid-onset pressure overload.[64,65] In contrast, partial mTORC1 suppression (produced by heterozygous deletion of mTORC1 or by rapamycin) in states of cardiac stress or injury ameliorates maladaptive hypertrophy and fibrosis and retards the development of heart failure (*Figure 1*).[66,67] The cardiac ageing that results from inflammasome activation is related to activation of the Akt/mTOR pathway,[20] and inhibition of the immunoproteasome system in the heart by rapamycin attenuates both inflammation and sympathetically-mediated hypertrophy.[68] Increases in oxidative stress in cardiomyocytes may cause premature senescence as a result of aberrantly increased Akt/mTOR signalling.[69] Sustained activation of Akt disrupts mitochondrial energetics and accentuates ageing-induced cardiac hypertrophy and myocardial contractile dysfunction[70,71]; mitochondrial function is normalized following mTOR inhibition.[72] The totality of these experimental observations explains why cardiac-specific overactivation of the Akt/mTOR pathway induces heart failure,[73] whereas suppression of Akt signalling ameliorates heart failure in experimental models.[74]

These findings supporting an effect of AKT/mTOR to promote cardiomyopathy are consistent with similar observations in the clinical setting. The myocardium in patients with a non-ischaemic cardiomyopathy shows aberrant activation of mTORC1; the intensity of this activation is associated with the severity of cardiac fibrosis and a poor prognosis.[75] In hypertensive patients with heart failure, there is an inverse relation between the degree of Akt activation and measures of cardiomyocyte senescence.[76] Akt activation may help to explain the insulin resistance that is characteristic of patients with chronic heart failure,[77] and mTORC1 up-regulation impairs cardiac function in obesity-related heart failure.[78] Activation of Akt in the human myocardium distinguishes the transition from well-compensated left ventricular hypertrophy to decompensated heart failure.[79]

Interplay of SIRT1/PGC-1α and Akt/mTOR and the intermediary role of adenosine monophosphate-activated protein kinase in modulating cardiomyocyte survival

The SIRT1/PGC-1α and Akt/mTOR pathways are highly interconnected, both at a molecular and physiological level (*Figure 2*). SIRT1 can modulate the transcription of Akt and mTOR as a result of its deacetylase activity,[80] and additionally, SIRT1 and PGC-1α can negatively regulate the transcription of Akt and directly interfere with Akt and mTOR.[81–84] At the same time, up-regulation of Akt leads to suppression of PGC-1α,[85] whereas inhibition of mTOR by rapamycin or Akt down-regulation leads to activation of SIRT1 and PGC-1α.[86–90] Interventions that retard organ-level ageing (e.g. glucose deprivation, cytoprotective drugs and genetic suppression of inflammasome activity) act to simultaneously up-regulate SIRT1/PGC-1α and suppresses the Akt/mTOR pathway.[20,91–93] Furthermore, drugs that act to directly up-regulate SIRT1 (e.g. resveratrol and SIRT1 activators) also serve to inhibit Akt/mTOR,[85,94–98] and conversely, suppression of SIRT1 leads to up-regulation of Akt/mTOR.[98] The interplay between SIRT1/PGC-1α and Akt/mTOR is greatly enhanced by the fact that both SIRT1 and Akt/mTOR influence common downstream targets.[99,100] Activators of SIRT1/PGC-1α and suppressors of Akt/mTOR can act synergistically or competitively to influence both lifespan as well as the cardiac response to ageing.[71,101] The set point for

the interplay of pathways that regulate growth and survival in cardiomyocytes is sensitive to both nutrients and the redox state.[2,3]

An important mediator of the interconnectivity between SIRT1 and Akt/mTOR is adenosine monophosphate-activated protein kinase (AMPK). AMPK discerns the balance between cytosolic levels of ATP and AMP, and it acts to promote ATP synthesis. Ageing is accompanied by suppression of AMPK,[102] and in turn, up-regulation of AMPK ameliorates the effects of cardiac ageing by mitigating fibrosis,[103] promoting ischaemic tolerance in the myocardium,[104,105] and reversing ageing-related impairment of angiogenesis and regenerative repair.[106,107] In general, caloric restriction activates both SIRT1, PGC-1α, and AMPK in parallel, and the molecular actions of AMPK support those of SIRT1/PGC-1α and oppose those of Akt/mTOR with respect to cellular homeostasis and survival (*Figure 2*). In addition, the actions of AMPK and SIRT1/PGC-1α reinforce each other[93]; the effect of AMPK to promote NAD+ leads to SIRT1 activation,[108] and AMPK can activate PGC-1α by phosphorylation.[109] Simultaneously, SIRT1 can augment the activity of upstream regulators of AMPK,[110] while inhibition of AMPK leads to suppression of PGC-1α.[93] In addition, AMPK can inhibit mTOR by an action on its upstream regulators as well as through a direct effect on components of the mTORC1 complex.[111,112] As a result of the interplay of these effects, AMPK augments the ability of SIRT1/PGC-1α signalling to oppose the actions of the Akt/mTOR pathway.

Mechanisms underlying the effects of SIRT1, AMPK, and Akt/mTOR on longevity and cardiac ageing and their role in the development of cardiomyopathy

What cellular mechanism underlies the ability of SIRT1/AMPK activation and Akt/mTORC1 suppression to prolong lifespan, slow cardiac ageing and mitigate the development of cardiomyopathy and heart failure? The accumulation of dysfunctional organelles and misfolded proteins drives the ageing process by increasing oxidative and endoplasmic reticulum stress, typically with secondary activation of proinflammatory pathways.[113,114] SIRT1/PGC-1α and AMPK signalling and Akt/mTORC1 inhibition can act directly to maintain organellar integrity, to promote antioxidant mechanisms and to interfere with activation of the inflammasome.[20,72,115–119] Akt/mTORC1 can also directly modulate the functions of the senescence-associated secretory phenotype.[58]

Role of autophagy in promoting longevity and cardiomyocyte survival

Yet, the most important mechanism by which SIRT1/PGC-1α/AMPK and Akt/mTORC1 prevents cellular stress and ageing is the disposal and neutralization of unwanted and injurious cytosolic constituents by the cellular housekeeping process of autophagy. Autophagy is an evolutionarily-conserved degradative pathway, which involves the encircling of dangerous cellular components by a double-membrane vesicle; its fusion with the lysosome allows degradative enzymes to destroy the vesicle's contents.[120] The process not only negates the effects of the injurious constituent, but it allows for recycling of the breakdown products, thus boosting cellular ATP.

Autophagic flux is the most important determinant of lifespan and cardiac ageing.[86,121–123] Normal and pathological ageing is accompanied by a reduced capacity for autophagy.[122,124–126] Mutation of essential autophagy genes induces degenerative changes in tissues that closely resemble those of ageing,[98] and inhibition of autophagy compromises the longevity effects of caloric restriction.[122,127,128] Loss of autophagy allows for the accumulation of deranged organelles and misfolded proteins, which are the major source of oxidative and endoplasmic reticulum stress in cardiomyocytes.[114,129] Conversely, enhancement of autophagic flux prevents the molecular and cellular features of ageing in the myocardium.[130] Pharmacological or genetic interventions that increase lifespan in model organisms act through stimulation of autophagy.[122,127]

How does autophagy delay ageing and promote cellular survival? The formation of autophagic vacuoles and their fusion with lysosomes disposes of misfolded proteins (as well as glucose and lipid intermediates), thus reducing endoplasmic reticulum stress. Furthermore, the autophagic clearance of deranged mitochondria and peroxisomes (referred to as mitophagy and pexophagy, respectively) is critical to the mitigation of oxidative stress.[131] (Cardiomyocytes are replete with mitochondria and peroxisomes, which underlie their enormous capacity to consume oxygen and generate reactive oxygen species.) Amelioration of oxidative and endoplasmic reticulum stress is essential to cardiomyocytes, since non-proliferating cells cannot utilize cell division to mediate dilution of intracellular debris or replace cells that have died.[122]

Role of SIRT1/AMPK and Akt/mTOR signalling in the modulation of autophagy

SIRT1/PGC-1α/AMPK and Akt/mTORC1 are the primary mediators of the ability of autophagy to prolong organismal longevity (*Figure 1*). The most important inducer of autophagy is caloric restriction, which acts to prolong organismal survival by signalling through both SIRT1/PGC-1α/AMPK as well as Akt/mTORC1.[122,132]

In states of glucose deprivation, AMPK promotes autophagy by directly activating several autophagy genes, including Ulk1,[133–136] whereas in states of nutrient surplus, mTOR prevents Ulk1 activation and disrupts the interaction between Ulk1 and AMPK.[108] Starvation does not prolong longevity if mTOR signalling is already suppressed,[128] and conversely, mTOR inhibition with rapamycin does not favourably affect survival if autophagy genes are already knocked down or out.[136] Conversely, SIRT1 deacetylases (and thereby activates) several autophagy genes[137]; SIRT1-mediated deacetylation of beclin 1 promotes autophagic flux[138]; and PGC-1α interacts with the E3 ubiquitin ligase Parkin to mediate mitophagy.[139,140] Importantly, the longevity effects of SIRT1 are mediated by its actions to promote autophagy,[141] and caloric restriction does not induce mitochondrial autophagy in aged animals if SIRT1 is absent.[142] The actions of SIRT1 to extend lifespan by promoting autophagy can be attenuated by activation of Akt.[71] Knockdown or knockout of autophagy genes abolishes the lifespan-prolonging effects of caloric restriction, resveratrol, or *Sir2* overexpression.[143] These observations, when considered

collectively, strongly support the critical role of autophagy in mediating the ability of SIRT1/PGC-1α/AMPK and Akt/mTOR signalling to influence organismal survival.

SIRT1/PGC-1α/AMPK and Akt/mTORC1 are also the primary mediators of the ability of autophagy to retard cardiac ageing (*Figure 1*).[144] The effects of inflammasome suppression to retard age-related deleterious changes in the heart are related to inhibition of Akt/mTOR and activation of SIRT1, leading to enhanced autophagic flux.[20] Ageing-related cardiomyocyte contractile dysfunction and loss of mitophagy are accompanied by suppression of PGC-1α and are ameliorated by mTOR inhibition with rapamycin and with direct Sirt1 activators.[71,102] AMPK activation restores autophagy in aged hearts,[145] and knockout of AMPK promotes cardiac ageing by suppressing autophagy, an action that is not alleviated by concurrent inhibition of Akt.[102] The effects of Akt to exacerbate cardiac ageing are dependent on its actions to suppress autophagy,[126,127] and the effects of mTOR inhibition with rapamycin to mitigate oxidative stress and ageing are mediated though enhanced mitophagy.[131] Similarly, the actions of caloric restriction to mitigate cardiac ageing are accompanied by simultaneous suppression of mTOR and enhanced autophagic flux.[146] These findings demonstrate the importance of autophagy in mediating the effects of SIRT1/PGC-1α/AMPK and Akt/mTOR on cardiomyocyte senescence.

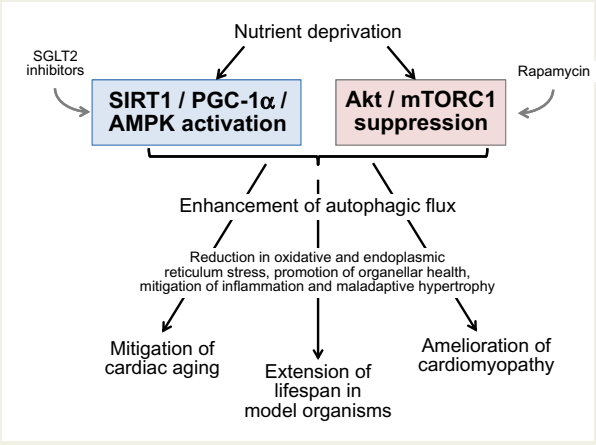
Importance of longevity gene signalling and autophagy modulation in the development and treatment of chronic heart failure

As a result of its critical role in maintaining cardiomyocyte health, autophagy plays a major role in the evolution and progression of heart failure. Diseases that lead to heart failure (as well as the heart failure state itself) mimic the ageing process, in that they are characterized by an increase in oxidative and endoplasmic reticulum stress, which is exacerbated by a striking impairment in the capacity of the heart to stimulate autophagy. Autophagic flux of cardiomyocytes is markedly impaired in cardiomyocytes derived from injured or failing hearts[147–149]; in return, pharmacological stimulation of autophagic flux can directly ameliorate oxidative stress and organellar dysfunction, thereby preventing or reversing cardiomyocyte dysfunction and mitigating the development of cardiomyopathy.[150–152] This deficiency in autophagic capacity in heart failure is related to the simultaneous impairment of SIRT1/PGC-1α and AMPK signalling[52,53,153] and enhanced activation of the Akt/mTORC1 pathway in cardiomyocytes.[147,151,154] These derangements in longevity gene signalling is seen both experimentally and clinically.

Interestingly, most treatments for heart failure and a reduced ejection fraction have been reported to exert favourable effects on SIRT1/AMPK and Akt/mTOR signalling, thereby, on autophagic flux. The action of angiotensin-converting enzyme inhibitors to mitigate the effects of angiotensin II may involve signalling through SIRT1[155,156] and enhancement of PGC-1α.[157] Angiotensin receptor blockers have been noted to promote autophagy,[158] effects that have been attributed to their effects to activate AMPK and inhibit Akt/mTOR.[159,160] Beta-blockade is accompanied by up-regulation of AMPK,[161,162] and carvedilol up-regulates PGC-1α[163] and appears to enhance autophagic flux through SIRT1 stimulation[164] and by mTOR inhibition.[165] Spironolactone activates SIRT1/AMPK in the heart,[166] and its action to inhibit Akt/mTOR signalling has been linked to its effect to promote autophagic flux.[167,168] PGC-1α activation can interfere with the deleterious actions of mineralocorticoid receptor activation.[169] Natriuretic peptides may activate AMPK,[170,171] and neprilysin may stimulate Akt/mTOR signalling and suppress PGC-1α.[172–174] Hydralazine up-regulates both AMPK and SIRT1, and thus, prolongs longevity in model organisms.[175] Digitalis glycosides induce autophagy (potentially by activating AMPK),[176] but they also activate Akt, which may limit the positive inotropic effect of these drugs.[177–180] The effect of cardiac resynchronization to effect reverse remodelling is accompanied by activation of autophagic flux and improvement in mitochondrial function.[181] Therefore, currently available treatments for heart failure appear to exert a consistently favourable influence on the interplay of SIRT1/AMPK and Akt/mTOR in a manner that promotes autophagy.

SGLT2 inhibitors have recently been shown to have favourable effects on the evolution and progression of heart failure in the presence and absence of Type 2 diabetes.[182] When the actions of SGLT2 are inhibited, the urinary loss of calories triggers systemic transcriptional reprogramming that closely mimics that seen during states of nutrient deprivation.[183,184] The depletion of tissue nutrients that follows glycosuria leads to activation of SIRT1 and AMPK and the suppression of Akt and mTOR.[183,184] It is therefore noteworthy that several SGLT2 inhibitors up-regulate SIRT1, PGC-1α and AMPK, while simultaneously inhibiting the Akt/mTOR pathway,[118,183–191] thus potentially explaining the action of these drugs to promote autophagy in diverse organs, including the heart.[192,193] The induction of autophagy may underlies the ability of SGLT2 inhibitors to mute oxidative stress, promote organellar integrity, suppress proinflammatory pathways, and ameliorate the course of experimental cardiomyopathy.[118,188,193–197] Importantly, because nutrient deprivation elicits a system-wide response, SGLT2 inhibitors can exert cardioprotective effects, even though SGLT2 is not expressed in the heart.[183,184] In addition, SGLT2 inhibitors may be able to bind directly to SIRT1 to activate its functions (*Figure 1*).[198]

Drugs that are well-characterized agonists and antagonists of SIRT1/AMPK and Akt/mTOR signalling may also prove to have favourable effects in the treatment of chronic heart failure. Metformin is an established agonist of AMPK (which also up-regulates PGC-1α), and it promotes autophagy and ameliorates the development of experimental diabetic and non-diabetic cardiomyopathy.[26,199–201] Epidemiological studies have suggested that the use of metformin may be accompanied by a reduced risk of heart failure, but these reports have been difficult to interpret, given the observational nature of these analyses and concerns that the reported benefits may have been related to an adverse effect of the comparator drugs rather than a favourable action of metformin.[202] Resveratrol (an activator of SIRT1)[18,29,45,203–208] and rapamycin and its analogues (inhibitors of mTORC1)[151,209–211] have also been shown to enhance autophagic flux and to ameliorate cardiomyopathy in experimental models. However, clinical trial evidence to support a benefit of



Take home figure Pathways that mediate and influence the interplay of lifespan extension, cardiac ageing, and the development of cardiomyopathy. Akt, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; mTORC1, mammalian target of rapamycin complex 1; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator-1 alpha; SIRT1, sirtuin-1.

metformin, resveratrol and rapamycin in patients with chronic heart failure is lacking.

Conclusions

Genes that modulate lifespan in model organisms play a crucial role in the regulation of cellular growth and survival as a result of their effects on the cellular housekeeping process of autophagy. Autophagic flux is exquisitely controlled by the interplay of the SIRT1/AMPK and Akt/mTOR pathways, which underlies the ability of caloric restriction and the redox state to modulate ageing (*Take home figure*). The interaction of these longevity genes is particularly important in cardiomyocytes, since these cells readily produce reactive oxygen species and their non-proliferating state impairs the dilution of cellular stress and the replenishment of senescent cells from stem cell niches. The impairment of autophagy that results from derangements in longevity gene signalling is likely to represent a seminal event in the evolution and progression of cardiomyopathy. Enhancement of autophagic flux may be an important feature of current and future treatments for heart failure.

Conflict of interest: M.P. has consulted for Abbvie, Actavis, Akcea, Amgen, AstraZeneca, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Johnson & Johnson, NovoNordisk, Pfizer, Sanofi, Synthetic Biologics, and Theravance.

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