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AMPK and cardiac remodelling

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Cardiac remodelling is generally accepted as a critical process in the progression of heart failure. Myocyte hypertrophy, inflammatory responses and cardiac fibrosis are the main pathological changes associated with cardiac remodelling. AMP-activated protein kinase (AMPK) is known as an energy sensor and a regulator of cardiac metabolism under normal and ischaemic conditions. Additionally, AMPK has been shown to play roles in cardiac remodelling extending well beyond metabolic regulation. In this review, we discuss the currently defined roles of AMPK in cardiac remodelling and summarize the effects of AMPK on cardiac hypertrophy, inflammatory responses and fibrosis and the molecular mechanisms underlying these effects. In addition, we discuss some pharmacological activators of AMPK that are promising treatments for cardiac remodelling.

AMP-activated protein kinase (AMPK), cardiac remodelling, hypertrophy, cardiac inflammation, cardiac fibrosis, AMPK activator

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INTRODUCTION

Cardiac remodelling is defined as genomic, molecular, cellular and interstitial changes that clinically manifest as changes in the size, shape and function of the heart in response to cardiovascular damage and pathogenic risk factors. Myocardial hypertrophy, inflammatory infiltration and fibrosis are the main pathologies associated with cardiac remodelling. The remodelling process involves the activation or suppression of numerous neurohumoral signalling pathways, thus affecting not only cardiomyocytes but also non-myocytes, including fibroblasts, endothelial cells, and a variety of immune cells (Gjesdal et al., 2011).

The heart is a circulating pump, and unlike other organs in the body, it requires high metabolic activity due to constant overloading. AMP-activated protein kinase (AMPK), a serine/threonine kinase comprising one catalytic subunit (α) and two regulatory subunits (β and γ), acts as a cellular "fuel gauge" to detect the intracellular ATP/AMP ratio and regulate cardiac metabolism. AMPK activity is mainly regulated by the phosphorylation of threonine 172 (Thr172) on its catalytic α subunit. In the heart, the α2 isoform is the most abundantly expressed catalytic subunit of AMPK and is predominantly distributed in cardiomyocytes, whereas AMPKα1 is mainly expressed in non-myocytes (Noppe et al., 2014). As a crucial energy sensor, AMPK has been shown to have a protective role in various cardiac pathophysiological processes, with the aim of restoring the energy balance (Dolinsky and Dyck, 2006). For example, during ischaemia, reduced oxygen levels induce an acute energy imbalance and AMPK activation, and AMPK promotes cellular glucose uptake by triggering the translocation of GLUT4 (glucose transporter 4, insulin-regulated glucose transporter)-containing membrane vesicles to the sarcolemma. In addition, AMPK also upreg-

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ulates glycolysis by accelerating its rate-limiting step, and AMPK facilitates fatty acid uptake and oxidation as oxygen delivery is restored during reperfusion. In response to mitochondrial damage during reperfusion, AMPK decreases the opening of the mitochondrial permeability transition pore (mPTP) to maintain mitochondrial respiratory capacity (Qi and Young, 2015). The role of AMPK in cardiac energy metabolism has been described in detail in the previous reviews (Kim and Dyck, 2015; Qi and Young, 2015). Additionally, AMPK has functions in the heart that extend beyond metabolic regulation. Here, we provide an overview of recent studies on the roles of AMPK in cardiac remodelling, particularly in cardiac hypertrophy, cardiac inflammation and cardiac fibrosis. We also discuss some widely used clinical AMPK activators that show substantial promise in preventing cardiac remodelling.

AMPK IN CARDIAC HYPERTROPHY

Cardiac hypertrophy, a major pathological process involved in cardiac remodelling, is characterized by increased cardiomyocyte size, a higher degree of sarcomere organization and enhanced gene transcription and translation levels, all of which are closely associated with energy metabolism (Tham et al., 2015). Hypertrophy initially serves as a compensatory mechanism to preserve cardiac output. However, if injurious stimuli persist, hypertrophy becomes maladaptive and impairs cardiac function, which progresses to heart failure. AMPK, a primary regulator of metabolic pathways, plays an essential role in a wide variety of cellular processes to protect against cardiac hypertrophy, mainly by regulating protein synthesis, cytoskeletal network expansion, transcriptional activity, energy supply, autophagy, endoplasmic reticulum (ER) stress and microRNA expression. The molecular mechanisms involved in these processes are listed in Figure 1.

Protein synthesis

Protein synthesis, an anabolic process, is required for cardiac hypertrophy. Two major pathways regulating protein synthesis are inhibited by AMPK. One is the eukaryotic elongation factor-2 (eEF2) kinase/eEF2 axis (Chan et al., 2004). eEF2 mediates peptide chain elongation and is phosphorylated and inactivated by eEF2 kinase. AMPK reportedly phosphorylates eEF2 by activating eEF2 kinase, resulting in the inhibition of protein synthesis. The other pathway that regulates protein synthesis and is inhibited by AMPK is the Akt/mam-

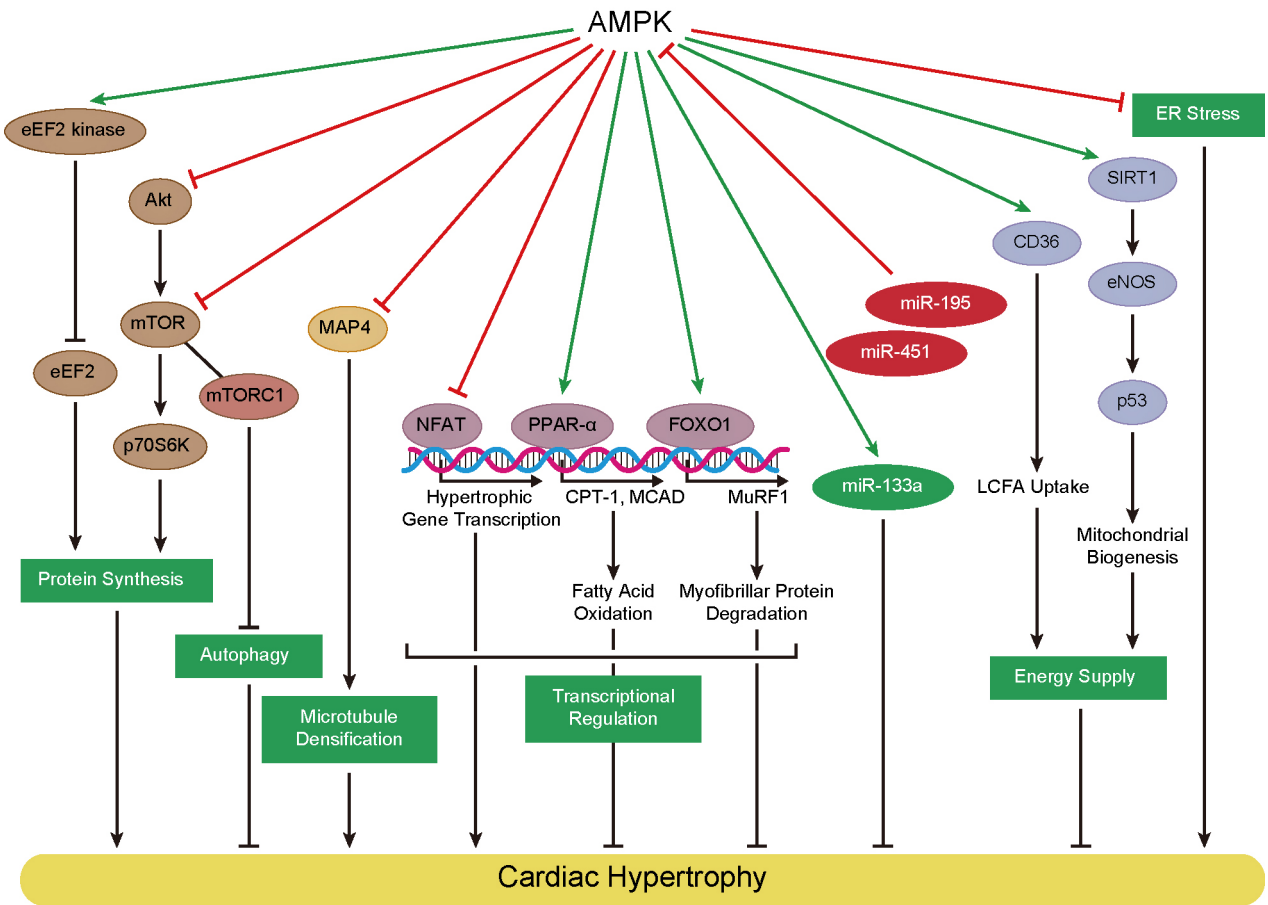

Figure 1 (Color online) The molecular mechanisms by which AMPK protects against cardiac hypertrophy. The lines with bars indicate inhibitory signals, and the lines with arrows indicate excitatory signals.

malian target of rapamycin (mTOR)/p70 ribosomal protein S6 kinase (p70S6K) pathway (Fu et al., 2011; Zarrinpashneh et al., 2008). The p70S6K protein participates in mRNA translation and cell growth. Compared with wild-type mice, p70S6K overstimulation and increased cardiac hypertrophy is observed in isoproterenol (ISO)-treated AMPKα2 knock-out mice. Based on these results, AMPKα2 inhibits protein synthesis in cardiac hypertrophy by downregulating p70S6K (Zarrinpashneh et al., 2008). As shown in our previous study, AMPK activation is required for metformin-mediated inhibition of pressure overload-induced cardiac hypertrophy by suppressing the Akt/mTOR pathway (Fu et al., 2011). In addition, nuclear Akt1 has recently been shown to be involved in the cardioprotective effects of AMPK on cardiac hypertrophy. AMPKα2 activation induced by CYP2J2 and its metabolites promotes the formation of the AMPKα2β2γ1-phospho-Akt1 complex, leading to the nuclear translocation of Akt1. In turn, nuclear Akt1 increases the expression of atrial natriuretic peptide (ANP), a known diuretic and vasodilatory factor, and ultimately attenuates cardiac hypertrophy (Wang et al., 2016a).

Microtubule densification

Cytoskeletal network expansion, specifically microtubule densification and proliferation, is another important characteristic of myocyte hypertrophy and is thought to contribute to cardiac contractile dysfunction. Microtubule-associated protein 4 (MAP4), which is upregulated in hypertrophied hearts, binds and stabilizes microtubules. The affinity of MAP4 for microtubules is reduced by the phosphorylation of MAP4 (Chinnakkannu et al., 2010). A previous study suggested a protective role for AMPKα2 in the response to hypertrophic stress by directly phosphorylating MAP4 and limiting the accumulation and densification of microtubules (Fassett et al., 2013).

Transcriptional regulation

AMPK also regulates cardiac hypertrophy at the transcriptional level. Overall, four mechanisms are reportedly involved in AMPK-mediated regulation of hypertrophy. Notably, AMPK protects against cardiac hypertrophy through the first three mechanisms, whereas AMPKα1 promotes cardiac hypertrophy through the last mechanism. (i) AMPK reduces the translocation of calcineurin-nuclear factor of activated T cells (NFAT) to the nucleus and subsequently suppresses hypertrophic gene transcription (Chan et al., 2008). (ii) AMPK upregulates the transcriptional activity of peroxisome proliferator-activated receptor-α (PPAR-α) via the extracellular signal-regulated kinase 1/2 (ERK1/2) signalling pathway (Meng et al., 2011) to promote carnitine palmitoyl transferase-1 (CPT-1) and medium-chain acyl-COA dehydrogenase (MCAD) expression, subsequently promoting fatty acid oxidation and normalizing myocardial energy metabolism (Meng et al., 2009). (iii) AMPK induces myofibrillar protein degradation through the activation of the atrophy-related forkhead box O1 (FOXO1)/muscle RING finger 1 (MuRF1) signalling pathway (Chen et al., 2010a). (iv) AMPKα1 specifically activates the protein kinase C zeta (PKCζ)/activator protein-1 (AP-1) pathway and subsequently exacerbates cardiac hypertrophy (Voelkl et al., 2016).

Energy supply

Elevated cardiac function during cardiac hypertrophy results in an increased energy demand and substrate utilization by producing glucose from fatty acids. CD36, which is expressed in cardiac myocytes and endothelial cells, translocates to the sarcolemma to mediate myocardial fatty acid uptake and maintain lipid homeostasis (Abumrad and Goldberg, 2016). CD36 plays a key role in the cardiac hypertrophy-associated energy supply. AMPK activation has been shown to increase long-chain fatty acid (LCFA) uptake in wild-type cardiomyocytes, but not in CD36 knock-out cardiomyocytes, suggesting that AMPK promotes CD36 expression to increase the fatty acid supply (Habets et al., 2007). Furthermore, AMPK activation increases the translocation of CD36 to the plasma membrane, which may be an important mechanism for the heart to respond to long-term metabolic demands, such as hypertrophy (Kim and Dyck, 2016). Thus, AMPK may improve the energy deficiency during cardiac hypertrophy by promoting CD36 expression.

Moreover, mitochondrial dysfunction is also involved in the impaired energy supply detected during cardiac hypertrophy. Endothelial nitric oxide (NO) synthase (eNOS) is a major regulator of mitochondrial biogenesis and function. Metformin-induced AMPK activation was recently shown to trigger the Sirtuin 1(SIRT1)/eNOS/p53 pathway and subsequently improve mitochondrial dysfunction in angiotensin II (Ang II)-induced cardiac hypertrophy (Hernández et al., 2014).

Autophagy

Autophagy has recently been proposed to play dual roles in cardiac hypertrophy. Constitutive autophagy maintains cardiac structure and function, whereas excess autophagy is detrimental to hypertrophied hearts by inducing cell death (Li et al., 2015). Autophagy regulates cellular homeostasis by degrading unwanted proteins, thereby clearing malfunctioned mitochondria and mitochondria-derived reactive oxygen species (ROS) and providing an energy supply. Therefore, autophagy is considered an adaptive mechanism during cardiac hypertrophy (Kubli and Gustafsson, 2014). mTOR, the key sensor of nutrient status, consists of two distinct complexes, mTORC1 and mTORC2. The mTORC1 inhibitor rapamycin promotes autophagy, but the role of mTORC2 during autophagy remains controversial (Gurusamy et al., 2010). The protective effects of AMPK

on pressure overload-induced cardiac hypertrophy were recently shown to be partially mediated by enhanced autophagy through the inhibition of mTORC1 signalling, but not mTORC2 signalling (Li et al., 2014). AMPK inhibits mTORC1 by phosphorylating tuberous sclerosis complex 2 (TSC2), a negative regulator of mTORC1 (Gwinn et al., 2008). Furthermore, AMPK-mediated autophagy is indispensable in maintaining cardiac homeostasis pathological changes in the heart caused by prolonged calorie restriction (Zheng et al., 2015).

In contrast, excessive autophagy activation triggers autophagic cell death and subsequently aggravates cardiac hypertrophy. Inhibition of the calcium/calmodulin-dependent protein kinase kinase β (CaMKKβ)-AMPK-mTOR pathway with a calcium-sensing receptor inhibitor has been suggested to contribute to autophagy suppression and cardioprotection during sustained pathological stimulation-induced cardiac hypotrophy (Liu et al., 2015; Liu et al., 2016).

ER stress

ER stress is characterized as an imbalance in ER homeostasis and ER dysfunction. Excess ER stress is involved in the development of cardiac hypertrophy by inducing cell death (Wang et al., 2017). AMPK activation by 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) attenuates hypoxia-induced ER stress in cardiomyocytes (Terai et al., 2005). In addition, prolonged ISO stimulation results in advanced ER stress and apoptosis in cardiomyocytes by inhibiting AMPK activation. In contrast, metformin protects cardiomyocytes from ISO-induced ER stress by activating AMPK (Zhuo et al., 2013). Intermedin, a novel calcitonin/calcitonin gene-related peptide family member, reportedly exerts a cardioprotective effect on hypertrophy by inhibiting ER stress and cardiomyocyte apoptosis in an AMPK-dependent manner (Lu et al., 2015). However, the mechanisms underlying the AMPK-mediated cardioprotective effects on ER stress are incompletely elucidated.

microRNAs

microRNAs are important regulators of the development of cardiac hypertrophy. During cardiac hypertrophy, AMPK interacts with several microRNAs, such as miR-133a, miR-451 and miR-195. Of these miRNAs, miR-133a plays a protective role in cardiac hypertrophy (Carè et al., 2007). Adiponectin, a circulating adipose-derived cytokine, increases miR-133a levels by activating AMPK and attenuates Ang II-induced cardiac hypertrophy (Li et al., 2016). In contrast, microRNAs also regulate the AMPK signalling pathway. Notably, miR-451 (Kuwabara et al., 2015) and miR-195 (Chen et al., 2012) expression are upregulated in hypertrophic cardiomyocytes, thus suppressing the activation of the liver kinase B1 (LKB1)/AMPK signalling pathway and subsequently exacerbating the progression of cardiac hypertrophy. Further studies are needed to identify the precise relationships between microRNAs and AMPK in various cardiovascular diseases.

AMPK isoform specificity

Although the activities of both AMPKα1 and AMPKα2 are elevated in cardiac hypertrophy, several studies have noted differences between the two catalytic subunits. In hypertrophied hearts, increased activity of the AMPKα1 isoform is associated with upregulation of the α1 protein, whereas the AMPKα2 protein is downregulated, despite its significantly increased activity (Tian et al., 2001). In addition, AMPKα2 knock-out mice display exacerbated cardiac hypertrophy and dysfunction in response to chronic pressure overload compared with wild-type mice. In contrast, an AMPKα1 deficiency has no detectable effects on cardiac structure and function (Xu et al., 2014). Furthermore, degradation of the gap junction protein connexin 43 was recently shown to be mitigated after pressure overload-induced cardiac hypertrophy in AMPKα1 knock-out mice, suggesting that the detrimental effects of AMPKα1 on hypertrophied hearts are mediated by impaired gap junction coupling (Alesutan et al., 2015). Further studies are needed to completely elucidate the distinct mechanisms by which AMPKα1 and α2 modulate cardiac hypertrophy.

AMPK IN CARDIAC INFLAMMATORY RESPONSES

Inflammatory responses are initiated by tissue injury during cardiac remodelling. Cardiomyocyte necrosis triggers an inflammatory cascade that clears injured cells and activates the repair process. However, excessive inflammatory responses may enhance cardiac injuries and prolong fibrosis. Anti-inflammatory and immunosuppressive effects of AMPK have been reported in various cell types and inflammatory/autoimmune diseases (Salt and Palmer, 2012). Here, we summarize studies on the roles of AMPK in cardiac inflammation.

Neutrophil infiltration

Neutrophils play a vital role in inflammatory responses to cardiac injury, such as ischaemia/reperfusion injury, by releasing oxidants, proteases and inflammatory products. Both acute AMPK activation (Soraya et al., 2012a) and chronic AMPK pre-activation (Soraya et al., 2015) by metformin alleviate cardiac remodelling by reducing peripheral neutrophil infiltration into the myocardial tissue following ISO-induced myocardial infarction (MI).

Neutrophil activation and oxidative stress activate Toll-like receptor (TLR) activation. TLR signalling induces the transcription of pro-inflammatory cytokine genes, which contribute to adverse cardiac remodelling. Among the TLRs expressed in the heart, TLR4 is the most frequently investigated isoform and is considered a therapeutic target for

myocardial diseases (Katare et al., 2017). TLR4 activation reportedly mediates left ventricular remodelling and leads to left ventricular dysfunction after MI (Timmers et al., 2008). Some studies have focused on the role of AMPK in TLR4 signalling in the heart. For example, both acute (Soraya et al., 2012b) and chronic (Soraya et al., 2014) AMPK activation by metformin have been shown to inhibit TLR4 expression and the resulting inflammatory cascade in infarcted myocardia. According to another study, AMPK activation by metformin markedly suppresses cardiac TLR4 activity and the inflammatory responses induced by lipopolysaccharides (Vaez et al., 2016).

Tumour necrosis factor-α (TNF-α) is a pro-inflammatory cytokine that displays increased expression during cardiac inflammatory responses, and AMPK has been shown to exert a powerful protective effect against TNF-α-induced cardiomyocyte necrosis and inflammatory cell infiltration in ischaemic myocardia (Peng et al., 2009).

eNOS signalling

Endothelial cells have been shown to play a role in cardiac inflammation. AMPK phosphorylates and activates eNOS through a calcium-independent mechanism (Li et al., 2004). In addition, the eNOS-NO pathway has been reported to protect against MI by inhibiting inflammation in a rat MI model (Chen et al., 2010b). Thus, AMPK inhibits MI-induced inflammation by activating the eNOS-NO pathway.

AMPK IN CARDIAC FIBROSIS

Cardiac fibrosis, which is characterized by a net accumulation of extracellular matrix (ECM) in the myocardium, is categorized as either reactive interstitial fibrosis or reparative fibrosis, according to the pathophysiological conditions (Travers et al., 2016). Reactive interstitial fibrosis is triggered in the absence of cell death and involves interstitial ECM deposition. Reparative fibrosis is related to cardiomyocyte necrosis, in which the dead myocardial tissue is replaced by collagen scar tissue. Excess ECM deposition increases myocardial stiffness and reduces ventricular compliance and diastolic dysfunction. The progression of fibrosis provokes ventricular dilation and systolic dysfunction, ultimately leading to heart failure. Several studies have reported the protective effects of AMPK on cardiac fibrosis.

Transforming growth factor β (TGFβ) signalling

TGFβ is considered the most potent and ubiquitously expressed profibrogenic cytokine. In the canonical signalling pathway downstream of TGFβ, Smads (mainly Smad2/3) translocate to the nucleus and promote the transcription of fibrosis-related genes. In addition, TGFβ activates non-Smad signalling pathways, including the ERK, c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (p38 MAPK) pathways (Zhang, 2017). As shown in our previous study, metformin inhibits pressure overload-induced cardiac fibrosis by inhibiting the TGFβ-Smad3 signalling pathway (Xiao et al., 2010). Furthermore, AMPK activation mainly targets TGFβ transcription by inhibiting hepatocyte nuclear factor 4 (HNF-4) expression in cardiac fibroblasts (Chen et al., 2017). ERK is a key protein kinase that regulates the growth and proliferation of cardiac fibroblasts. The activation of AMPK with AICAR inhibits the growth and proliferation of cardiac fibroblasts by inhibiting ERK (Du et al., 2008).

TGFβ also promotes the transdifferentiation of fibroblasts into myofibroblasts, which express α-smooth muscle actin (α-SMA) and play a key role in the synthesis and release of ECM proteins. However, the function of AMPK in myofibroblast differentiation has been disputed. An AMPKα1 deficiency leads to increased cardiac fibroblast proliferation and decreased myofibroblast maturation in infarcted myocardia, thereby resulting in the formation of immature scars and adverse cardiac remodelling (Noppe et al., 2014). The potential mechanisms underlying these effects include downregulation of the TGFβ-p38 MAPK pathway and the reduced expression of lysyl oxidase (LOX), a critical factor involved in collagen cross-linking. Thus, AMPKα1 promotes myofibroblast activation and scar formation in post-MI-induced cardiac fibrosis. Consistent with these results, AMPK activation by AICAR has been shown to improve scar formation in MI areas by increasing LOX expression in aged mice (Cieslik et al., 2013). In contrast, AMPK activation by C1q/TNF-related protein 3 (CTRP3), a novel adipokine, has been shown to inhibit TGFβ-Smad3-mediated myofibroblast activation in a rat MI model (Wu et al., 2015). Aucubin, which is extracted from medical plants, has recently been described to activate AMPK-mTOR signalling and suppress TGFβ1-mediated myofibroblast activation (Xiao et al., 2017). In addition, metformin also reportedly attenuates Ang II-induced myofibroblast differentiation by inhibiting the protein kinase C (PKC)-NADPH oxidase (NOX) pathway (Bai et al., 2013). However, researchers have not clearly determined whether AMPKα2 contributes to the inhibitory effects on myofibroblast activation and further investigations are required.

Oxidative stress

ROS play key roles in cardiac fibrosis, and ROS scavenger treatments prevent cardiac fibrosis (Richter and Kietzmann, 2016). Additionally, NOX is the primary source of ROS in the heart. As shown in our recent study, exercise training reduces NOX4 levels, limits ROS production, and subsequently inhibits ISO-induced cardiac fibrosis by activating AMPK (Ma et al., 2015). In addition, PPAR-α reportedly decreases tissue fibrosis at least in part by reducing ROS levels (Diep et al., 2002). Adiponectin also reportedly protects against Ang

II-induced cardiac fibrosis via AMPK-dependent PPAR-α activation and reduced ROS production (Fujita et al., 2008).

SIRTs

SIRT proteins are a family of histone deacetylases that regulate metabolism. SIRT1 is a member of the SIRT family that reduces ROS-induced cardiac injury by forming a positive feedback loop with AMPK (Chong et al., 2012). SIRT1 deacetylates the AMPK kinase LKB1 and then activates AMPK (Lan et al., 2008). AMPK, in turn, increases the NAD^+/NADH ratio to mediate the activation of SIRT1 (Ruderman et al., 2010). In addition, SIRT3 (Lombard and Zwaans, 2014) and SIRT6 (Wang et al., 2016b) also reportedly reduce oxidative stress through an AMPK-dependent pathway.

PHARMACOLOGICAL AMPK ACTIVATORS

Numerous pharmacological AMPK activators, including natural products or extracts or synthetic compounds, have been developed (Salt and Hardie, 2017), many of which have proven effects on protecting against cardiovascular diseases, including metformin, statins, resveratrol, berberine, AICAR and A-769662 (Daskalopoulos et al., 2016; Salt and Hardie, 2017). However, AICAR and A-769662 have in the limitations of poor metabolism or poor oral availability (Grahame Hardie, 2016). In the next section, we discuss the AMPK activators that are widely used in the clinic or are therapeutically promising treatments for cardiac remodelling.

Metformin

Metformin is a synthetic biguanide derivative that was originally extracted from the French lilac *Galega officinalis* and is currently used as the first-line drug for the treatment of type 2 diabetes mellitus. Furthermore, other properties of metformin in addition to glycaemic control have been clarified in subsequent studies. Metformin was first shown to activate AMPK in 2001 (Zhou et al., 2001). Studies by our group and other researchers have shown that metformin reduces cardiac fibrosis and cardiac hypertrophy through AMPK-dependent pathways, as discussed above. In our previous study, metformin inhibited TGFβ1 production by targeting HNF4α and inhibited cardiac fibrosis through an AMPK activation-dependent mechanism (Chen et al., 2017). Nevertheless, metformin also reportedly protects against cardiac remodelling through an AMPK-independent mechanism (Xiao et al., 2010; Xu et al., 2014). According to our data, metformin directly interacts with TGFβ1, therefore inhibiting the TGFβ1 downstream signalling pathway through an AMPK-independent pathway (Xiao et al., 2016). Therefore, metformin inhibits the TGFβ1 pathway and cardiac remodelling through both AMPK-dependent and AMPK-independent mechanisms.

The mechanism by which metformin activates AMPK is now well accepted to occur via the inhibition of the mitochondrial respiratory chain complex I and ATP synthesis (Grahame Hardie, 2016). Metformin has a few adverse effects (a very low incidence of lactic acidosis) and excellent cardioprotective effects. Many clinical trials have been performed to examine the efficacy of metformin as a treatment for coronary heart disease and MI in both diabetic and nondiabetic subjects (Nesti and Natali, 2017). Notably, the ongoing MET-REMODEL trial aims to investigate the efficacy of metformin in promoting the regression of left ventricular hypertrophy in patients with coronary artery disease (Mohan et al., 2015).

Statins

Statins are 3-hydroxy-3-methylgutaryl-coenzyme A (HMG-CoA) reductase inhibitors used to lower cholesterol levels in clinic (Wang et al., 2012). In addition, statins also have pleiotropic effects beyond their cholesterol control effects. The administration of atorvastatin, one of the most widely prescribed statins, reportedly attenuates the hypertrophic, fibrotic and inflammatory responses after MI in rats (Reichert et al., 2016). The clinical efficacy of statin treatment in decreasing cardiovascular mortality and morbidity has been well proven in several clinical trials (Heart Protection Study Collaborative Group, 2002; Foody et al., 2006; Lewington et al., 2007). Indeed, statins have been shown to attenuate cardiac fibrosis via AMPK activation (Choi et al., 2017; Hermida et al., 2013). eNOS signalling pathway is identified to maintain cardiovascular homeostasis by controlling NO bioavailability. The beneficial effects of statins on cardiovascular diseases are primarily suggested to be the result of eNOS activation via an AMPK-dependent manner (Chen et al., 2009; Izumi et al., 2009; Sun et al., 2006).

The mechanism by which statins activate AMPK is indirect and independent of the AMP/ATP ratio increase (Wong et al., 2009). Statins have been shown to activate AMPK by increasing ROS-dependent PKCζ activity (Choi et al., 2008). Further studies are required to identify the protective effects and mechanisms of statins in cardiovascular diseases.

Resveratrol

Resveratrol is a natural polyphenolic molecule that is found in several plant species, including red grapes, berries and peanuts (Zordoky et al., 2015). Resveratrol reportedly inhibits protein synthesis and protects against cardiac hypertrophy through an AMPK-dependent pathway (Chan et al., 2008). Nevertheless, at low concentrations, resveratrol inhibits hypertrophy through an AMPK-independent mechanism that reduces oxidative damage (Zordoky et al., 2015) and promotes autophagy (Wang et al., 2015). Indeed, resveratrol also exerts anti-fibrotic effects on cardiac remodelling,

but evidence proving whether these effects are mediated by AMPK is not available (Daskalopoulos et al., 2016).

Resveratrol was recently shown to activate AMPK through at least two mechanisms (Lan et al., 2017). The first is an energy-dependent mechanism in which resveratrol inhibits ATP synthesis, similar to metformin. The second is an energy-independent mechanism of SIRT1-LKB1 activation. Although preclinical animal studies have achieved impressive results in the treatment of cardiovascular diseases, the low bioavailability of resveratrol creates questions regarding its translation into clinical studies (Zordoky et al., 2015). Various strategies, including new resveratrol analogues and drug-delivery systems, have been attempted and hold promise for realizing the true potential of resveratrol as a clinical therapy (Sung and Dyck, 2015).

Berberine

Berberine, another polyphenol, is widely used to treat diarrhoea. It also reportedly activates AMPK by inhibiting the mitochondrial respiratory chain and decreasing ATP synthesis (Grahame Hardie, 2016). Berberine treatments have been shown to improve cardiac dysfunction in diabetic rats and attenuate cardiomyocyte hypertrophy by activating AMPK (Chang et al., 2015). Moreover, berberine reportedly exerts anti-fibrotic effects by inhibiting cardiac fibroblast proliferation, transformation and collagen synthesis through the AMPK-mTOR-p70S6K signalling pathway (Ai et al., 2015). Metformin, statins and berberine have been used as medicines by humans for decades or even centuries (Grahame Hardie, 2016). These traditional medicines exerts new treatment effects, which are well worth exploring in the future.

Notably, the pharmacological activators of AMPK discussed above also have many AMPK-independent effects. On one hand, these activators may exerts more advantageous therapeutic effects on cardiovascular diseases. Indeed, as shown in our previous study, metformin inhibits cardiac fibrosis through both AMPK-dependent and -independent pathways (Chen et al., 2017; Xiao et al., 2010; Xiao et al., 2016). On the other hand, these activators inevitably induce some "off-target" effects. For instance, the AMPK activator A-769662 directly inhibits Na^+-K^+-ATPase activity and decreases the cell surface levels of sodium pumps in skeletal muscle cells, which is independent of AMPK activation (Benziane et al., 2009). Therefore, new synthetic or natural extract-derived AMPK activators should more directly and specific target AMPK.

DISCUSSION AND CONCLUSION

In conclusion, in addition to its regulatory roles in metabolism, AMPK controls the phenotype and function of nearly all cells involved in cardiac remodelling (Figure 2). Briefly, AMPK critically prevents cardiomyocyte hypertrophy and promotes autophagy. Moreover, AMPK exerts anti-inflam-

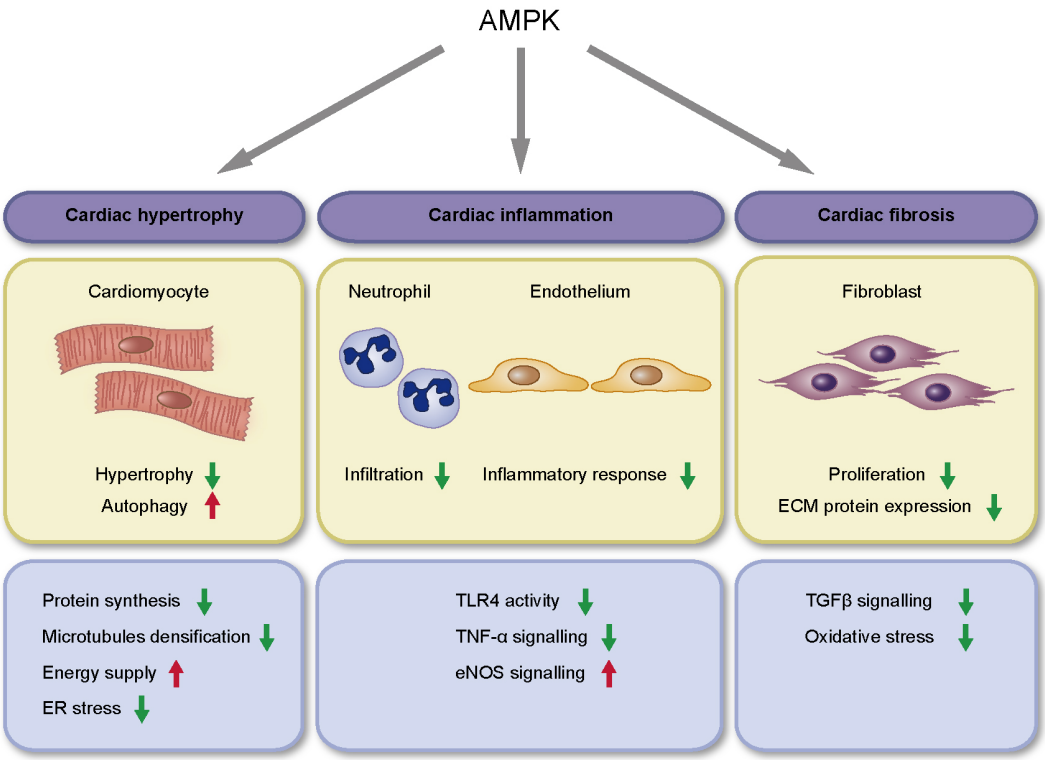

Figure 2 (Color online) The cellular effects and mechanisms by which AMPK protects against cardiac hypertrophy, cardiac inflammation and cardiac fibrosis. Red arrow, upregulation; green arrow, downregulation.

matory effects by targeting TLR4 and TNF-α signalling and enhancing eNOS signalling. Furthermore, AMPK inhibits fibroblast proliferation and ECM synthesis by suppressing the TGFβ signalling pathway and ROS production.

We summarized the roles of AMPK in three typical pathologies of cardiac remodelling: cardiac hypertrophy, cardiac inflammation and cardiac fibrosis. The mechanisms involved are shown in Figure 2. However, several crucial questions remain to be addressed. What is the precise mechanism underlying the anti-inflammatory effects of AMPK? Are the protective effects of AMPK on cardiac remodelling isoform-specific? Studies addressing these questions will provide important information for researchers aiming to develop AMPK-targeted therapies for cardiac remodelling.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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