Curr Heart Fail Rep (2012) 9:164–173
DOI 10.1007/s11897-012-0102-z

INVESTIGATIVE THERAPIES (J.-L. BALLIGAND, SECTION EDITOR)

AMP-activated Protein Kinase in the Control of Cardiac Metabolism and Remodeling

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Published online: 6 July 2012

Abstract The AMP-activated protein kinase (AMPK) can be firstly considered as a cellular fuel gauge. AMPK rapidly senses energy deprivation and orchestrates a metabolic response to maintain an acceptable energy level required for cell survival under such adverse condition. Its protective role during myocardial ischemia has been deeply documented. More recently, it has been shown that the role of AMPK extends to several nonmetabolic effects related to other cardiac pathologies comprising diabetic cardiomyopathy, cardiac hypertrophy, and heart failure. Here, we briefly review the different roles played by AMPK in the control of cardiac metabolism and function under normal and pathological conditions. The potential cardioprotective actions of AMPK and the relative importance of its energetic and nonmetabolic effects in these mechanisms are deeply discussed.

Keywords AMP-activated protein kinase · AMPK · Angiogenesis · Cardiac remodeling · Diabetic cardiomyopathy · Energy sensor · Extracellular matrix · Fibrosis · Heart failure · Hypertrophy · Insulin resistance · Metabolism · Myocardial infarction · Myocardial ischemia · Protein synthesis

Introduction

The AMP-activated protein kinase (AMPK) is a cellular fuel gauge that rapidly senses energy deprivation. Once activated, AMPK orchestrates a metabolic response to maintain acceptable adenosine triphosphate (ATP) level required for cell survival under such adverse condition. AMPK is a well-conserved eukaryotic heterotrimeric protein kinase composed of one catalytic (α) and two regulatory (β and γ) subunits (see [1] for review). The serine/threonine kinase activity of AMPK is supported by the α subunit, which contains, in its activation loop, a threonine residue (Thr172) whose phosphorylation by upstream kinases is required for AMPK activation. The β subunit includes a C-terminal region responsible for its association with α and γ subunits and a central region that allowed AMPK complex to bind glycogen. The γ subunit contains three adenine nucleotide-binding sites; two of them can bind adenosine monophosphate (AMP) or ATP in a mutually exclusive manner, whereas the third one binds a non-exchangeable AMP molecule. Binding of AMP to γ subunit induces AMPK activation via a complex mechanism involving direct allosteric stimulation and Thr172 phosphorylation by the protein kinase LKB1 (a tumour suppressor whose germline mutations in humans are the cause of Peutz-Jeghers syndrome). It was originally proposed that AMP binding promoted AMPK phosphorylation by LKB1. However, more recent works revealed that LKB1 is constitutively active and that the increase in AMPK phosphorylation results from the AMP-dependent inhibition of the constitutive dephosphorylation of Thr172 by protein phosphatase [2]. Finally, ATP can exchange with AMP in two adenine nucleotide-binding sites, leading to inhibition of the allosteric stimulation and protection from dephosphorylation by AMP. A second AMPK activation pathway, independent of the cellular energy state, has been described and involved Thr172 phosphorylation by the calcium/calmodulin-dependent protein kinase kinase β (CamKKβ). This pathway, triggered by an increase in calcium concentration, has been reported in smooth muscle and endothelial cells but not in cardiomyocyte [3, 4].

Each AMPK subunit exists under several isoforms encoded by different genes, two for α (α1 and α2) and β

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(β1 and β2) subunits and three for γ subunit (γ1, γ2, γ3), giving 12 possible combinations of holoenzyme (see [1] for review). Expression of these isoforms differs from one organ to another. The AMPKα2 is the most abundant catalytic subunit in murine heart whereas AMPKα1 and AMPKα2 seem to be equally expressed in human organ. By using LKB1 knockout mice, we demonstrated that cardiac AMPKα2 activity is exclusively dependent of LKB1 whereas a still unidentified AMPK kinase is responsible for AMPKα1 activation [2]. Even if the upstream pathway involved in their activation looks different, the respective roles of the two catalytic AMPKα isoforms remain largely unclear. Indeed, all the numerous AMPK substrates discovered so far seem to be indiscriminately phosphorylated by both isoforms.

It is well established that cellular energy is a key regulator of the AMPK system. Cellular energy imbalance occurring during metabolic stresses results in the increase in intracellular AMP/ATP ratio and, so, to AMPK activation. Once activated, AMPK acts to maintain cellular energy balance, switching on catabolic pathways that produce ATP, while switching off anabolism that consumes ATP [1, 5]. This contributes to cell survival in the absence of oxygen.

AMPK, Cardiac Metabolism, and Ischemia/Reperfusion Injury

The regulation of energy metabolism is one of the key roles of AMPK in the heart. The heart is a simple circulating pump. However, this cardiac pump has to permanently adapt its function and, so, its energy consumption to the circulating substrates, hormones, and oxygen availability. Moreover, in healthy heart, the amount of energy necessary to sustain contractile function, excitation/contraction coupling process, and metabolism is considerable. A human heart produces and immediately consumes 3.5 to 5 kg of ATP each day [6]. This ATP is mainly generated by mitochondrial oxidation of fatty acids (for 60–80 %) and glucose/pyruvate (for 20–40 %) requiring a continuous flux of oxygen [7]. The reduction of the oxygen flux, for example during myocardial ischemia, will instantly induce an energetic imbalance, an increase in AMP/ATP ratio, and AMPK activation. Once activated, AMPK promotes glycolysis, the sole ATP-producing pathway under anaerobic conditions by phosphorylating Akt substrate of 160 kDa (AS160) and 6-phosphofructo-2-kinase (PFK-2) (Fig. 1). AS160 is the guanosine triphosphatase (GTPase)–activating protein of the small G protein Rab involved in the translocation of the vesicles containing the glucose transporter GLUT4 to the sarcolemmal membrane [7]. The AMPK-mediated phosphorylation and inhibition of AS160 activates Rab, and then stimulates glucose transport to fuel anaerobic glycolysis [8, 9]. The phosphorylation of PFK-2 by AMPK induces its activation, leading to the synthesis of fructose 2,6-bisphosphate, the most potent stimulator of 6-phosphofructo-1-kinase, the key regulating enzyme of glycolytic flux [10]. AMPK, by increasing glycolytic ATP production, clearly plays a cardioprotective role during ischemic episodes. However, AMPK could play a deleterious role in the reperfused heart. Indeed, during early reperfusion, the still existing AMPK activation helps fatty acid oxidation to predominate over glucose oxidation by phosphorylating and inactivating acetyl-CoA carboxylase, the enzyme that catalyzes the formation of malonyl-CoA, an inhibitor of fatty acid import into mitochondria [11]. Fatty acid oxidation, occurring in parallel to the still present glycolytic stimulation, should promote a deleterious uncoupling of glucose oxidation and glycolysis [12]. Several studies using different transgenic animal models have been performed to definitively confirm the protective or deleterious action of AMPK during an ischemia/reperfusion episode [13–15, 16••, 17•, 18, 19] (Table 1). In mice lacking AMPKα2 or expressing a dominant-negative AMPK isoform, the ischemia-induced stimulation of glucose uptake and glycolysis is greatly inhibited [13–15, 19]. This decrease in metabolic response leads to major ATP depletion and is accompanied by a more rapid and severe ischemic contracture and a greater infarct size. During reperfusion, even if stimulation of fatty acid oxidation is absent in these mouse hearts, there is an obvious delayed or poorer post-ischemic contractile recovery [14, 15]. These results, taken together, demonstrate that the protective effect of AMPK during ischemia prevails over its putative deleterious action during reperfusion. Moreover, Kim and collaborators [17•] recently showed that pharmacological overactivation of AMPK could be a novel strategy to protect the heart against ischemia. Indeed, a pre-treatment of the heart with the new specific AMPK activator A-769662 preserves energy charge during ischemia, delays the onset of ischemic contracture, reduces infarct size, and allows a better recovery of contractile function during post-ischemic reperfusion.

AMPK, Diabetes, Insulin Resistance, and Diabetic Cardiomyopathy

There is compelling evidence from clinical and epidemiological studies indicating that diabetes increases the risk for cardiac dysfunction and heart failure (HF) independently of coronary artery disease and hypertension [20]. Different factors, including myocardial insulin resistance and decrease in glucose uptake and utilization in favor to fatty acid oxidation, participate in the development of this diabetic cardiomyopathy. In this light, therapies that normalize insulin sensitivity and favor glucose metabolism have been

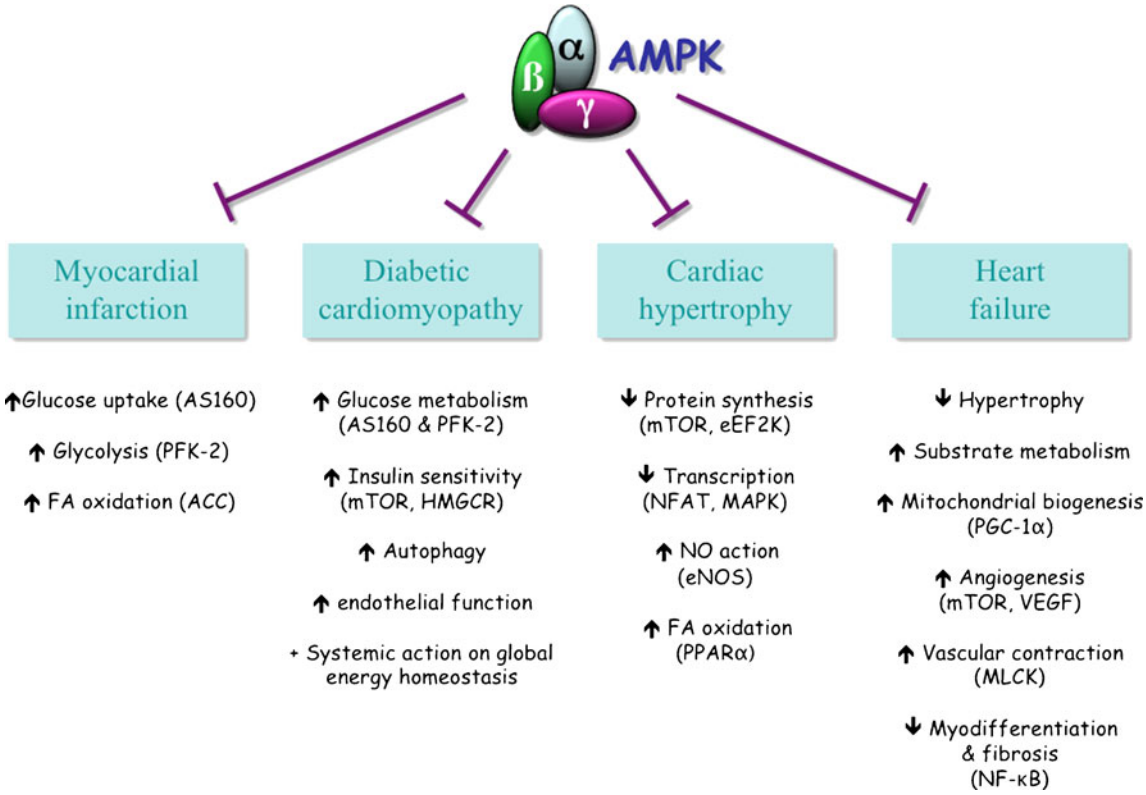

Fig. 1 Main molecular mechanisms involved in the cardioprotective effects of AMPK *PFK-2* 6-phosphofructo-2-kinase; *FA* fatty acids; *ACC* acetyl-Coa carboxylase; *mTOR* mammalian target of rapamycin; *HMGCR* 3-hydroxy-3-methylglutaryl-CoA reductase; *eEF2K* elongation factor 2 kinase; *NFAT* calcineurin-nuclear factor of activated T cells; *MAPK* mitogen-activated protein kinase; *eNOS* endothelial nitric oxide synthase; *PPARα* peroxisome proliferator-activated receptor alpha; *PGC-1α* peroxisome proliferator-activated receptor γ co-activator 1α; *VEGF* vascular endothelial growth factor; *MLCK* myosin light chain kinase; *NF-κB* nuclear factor kappa beta

proposed to reduce prevalence of cardiac complications of diabetes. Due to its nature, AMPK could play an important role in such therapies (Fig. 1). First, by stimulating cardiac glucose uptake and glycolysis independently of insulin, AMPK can bypass insulin resistance and increase glucose metabolism. Second, it has been shown at the beginning of the past decade that AMPK can be activated by the anti-diabetic drug metformin [21]. Since that time, numbers of studies have used AMPK activators to investigate its putative action against insulin resistance and diabetes (see [1] for review). Concerning the heart, AMPK activation by metformin or other activators unrelated to diabetic drugs, like the oxidative phosphorylation inhibitor oligomycin, is able to increase insulin sensitivity in insulin-resistant cardiomyocytes [22, 23•, 24, 25]. The restoration of an effective insulin response by AMPK could be explained by its action on an insulin negative feedback loop mechanism and on cholesterol metabolism. Indeed, AMPK is known to inhibit the mammalian target of rapamycin (mTOR)/p70 ribosomal S6 protein kinase (p70S6K) pathway. This pathway is located downstream of insulin and different growth hormones and has been firstly described in the regulation of protein synthesis (see next chapter). More recently, it has been shown that the mTOR/p70S6K pathway participates in the phosphorylation and inhibition of the insulin receptor substrate-1 (IRS1) inducing the silencing of the insulin response in a negative feedback manner [26]. This process has been proposed to participate in the development of insulin resistance under hyperinsulinemia and diabetes [27]. By inhibiting mTOR/p70S6K, AMPK prevents the negative feedback loop to operate and, so, increases cardiac insulin signaling [23•]. However, this mechanism seems not sufficient to explain all the insulin-sensitizing effects of AMPK, including the increase in glucose uptake [23•]. Recently, it has been demonstrated that the AMPK-mediated inhibition of cholesterol synthesis via the regulation of 3-hydroxy-3-methylglutaryl-CoA reductase decreases membrane cholesterol content and participates in the increase in insulin-mediated glucose transport in myotubes [28]. Beyond metabolism, AMPK also protects the diabetic heart by enhancing autophagy [29] and by preserving endothelial function [30, 31]. Moreover, as for nondiabetic hearts, pharmacological activation of AMPK protects the diabetic heart against ischemia/reperfusion injury [32]. Finally, the protective action of AMPK in the diabetic heart should be connected to its other beneficial effects in other organs like liver, muscle, and

Table 1 Cardiac function in AMPK transgenic and knockout mice submitted to different pathologies and treatments

Animal model[a]	Model of pathology	Treatment	Downstream effects	Study
AMPKα2-DN (D157A)	No flow ischemia	–	↓ Glucose uptake More rapid ischemic contracture	Xing et al. [19]
	MI (acute)	Metformin	(Present in WT not in DN) ↓Infarct size	Calvert et al. [18]
AMPKα2-DN (D157A) (+NOS3-KO)	MI (chronic)	Metformin	(Present in WT not in DN) Preserved energy charge Preserved cardiac function	Gundewar et al. [16••]
AMPKα2-DN (K45R)	No flow ischemia	–	↓ Glucose uptake, ↓ Glycolysis ↓ Cardiac function recovery	Russell et al. [15]
	MI (acute)	A-769662	(Present in WT not in DN) Preserved energy charge Delayed ischemic contracture ↓ myocardial apoptosis/necrosis	Kim et al. [17•]
AMPKα2-KO	POH	–	↑ Systolic dysfunction ↑ Hypertrophy, ↑ fibrosis	Zhang et al. [44]
	–	Isoproterenol	↑ Systolic dysfunction ↑ Hypertrophy, ↑ fibrosis	Zarrinpashneh et al. [43]
	No flow ischemia	–	Rapid ischemic contracture ↓ Glycogen content ↓Glycolytic flux No effect on cardiac recovery	Zarrinpashneh et al. [13]
	Low-flow ischemia	–	↓ Glucose uptake Rapid ischemic contracture Delayed post-ischemic recovery	Carvajal et al. [14]
LKB1-KO (cardiac specific)	–	–	↑ Systolic dysfunction ↑ Hypertrophy, ↑ fibrosis	Ikeda et al. [46]

AMPK AMP-activated kinase ; *MI* myocardial infarction; *WT* wild-type; *DN* dominant-negative; *POH* pressure-overload hypertrophy

[a] Two different forms of dominant-negative transgenic mice have been used. They are named AMPKα2-DN (D157A) and AMPKα2-DN (K45R) in relation to the mutation used to abolish AMPK activity

hypothalamus to correct global energy homeostasis at the whole body level [1].

AMPK, Protein Synthesis, and Cardiac Hypertrophy

Because protein synthesis is an anabolic pathway that consumes a significant quantity of ATP, a reduction of its rate by AMPK could be considered as an efficient mechanism to spare energy during myocardial ischemia. The regulation of protein translation by AMPK has been firstly described in hepatocytes [33, 34]. AMPK inhibits the mTOR/p70S6K pathway by acting on two mTOR partners, Raptor and tuberous sclerosis complex-2 [35, 36]. p70S6K is involved in the translation of the 5′-TOP mRNAs, which encode ribosomal proteins and elongation factors. In addition to p70S6K, mTOR also regulates the eukaryotic initiation factor-4E binding protein-1 (4E-BP1) involved in the initiation of translation (see [7] for review). AMPK also inactivates the eukaryotic elongation factor 2 (eEF2) pathway required for peptide chain elongation via the regulation of the eEF2 kinase [34, 37]. Inhibition of these pathways by AMPK during myocardial ischemia has been deeply described [17•, 38, 39].

Inasmuch as cardiac hypertrophy is known to be associated with an increase in protein synthesis, it was rapidly postulated that AMPK activation should inhibit the development of this pathology (Fig. 1). Pharmacological AMPK activation in cultured cardiomyocytes modulates p70S6K and eEF2 phosphorylation, inhibits protein synthesis, and prevents cell hypertrophy [40, 41]. AMPK also participates in the antihypertrophic effect of calorie restriction in a hypertensive rat model [42•]. On the other hand, cardiac hypertrophy induced by isoproterenol [43] or aortic constriction [44] is more pronounced in AMPK-deficient mice (Table 1). In correlation to these reports, the hypertrophic response is amplified in adiponectin knockout mice, which are characterized by a diminished AMPK activity [45•]. Moreover, the cardio-specific deletion of LKB1, its upstream kinase, led to hypertrophy and correlated with an activation of mTOR signalling [46]. The hypertrophic phenotype could be reversed by overexpressing a constitutively

active form of AMPK or by inhibiting mTOR with its specific inhibitor rapamycin. Recently, it has been shown that AMPK also negatively regulates cardiac hypertrophy by inhibiting mitogen-activated protein kinase [47] and calcineurin-nuclear factor of activated T cells [48] pathways and by promoting iatrogenic [49], nitric oxide [42•], and peroxisome proliferator-activated receptor (PPAR) α [50] signaling.

AMPK and Cardiac Remodeling

Left Ventricular Remodeling: From Hypertrophy to Failure

Myocardial remodeling is an essential adaptive process through which the heart responds to mechanophysical and metabolic stresses (see [51] for review). As already mentioned, distribution of blood and perfusion of all organs being the major determinants of regulation of cardiac work, any compensatory mechanism will be proportionate to the needs of the whole organism. Cardiomyocytes are providing the contractile force of the heart and undergo hypertrophy to compensate for cardiac dysfunction. Hypertrophy results from at least two separate but possibly interdependent stimuli: the stretch imposed on the chamber wall (and therefore on the individual myocytes), and neurohumoral stimulation by agents such as catecholamines and vasoactive peptides (eg, angiotensin II or the endothelins) [52]. However, prolonged and severe hypertrophy is a risk factor for arrhythmias, sudden death, and HF [53]. The molecular mechanisms that mediate the transition from compensated hypertrophy to decompensated HF remain poorly understood. The pathological transition is probably multifactorial and even though metabolic disturbances are considered to play a significant role, nonmuscle cells residing in the interstitium are also important players in both cardiac hypertrophy and HF [54–58]. Indeed, the hypertrophied myocardium is characterized by important structural changes involving a reinforcement of the fibrous scaffold of the heart, which is sustained by deposition of collagen and other extracellular matrix (ECM) proteins between individual myocytes [59]. The turnover regulation of ECM components constitutes the primary role of cardiac fibroblasts (CFs) [54, 55]. They account for approximately 26–63 % of cells within the myocardium of mouse and rat, respectively [60]. Myocardial fibrosis contributes to HF by increasing myocardial stiffness and reducing pumping capacity [61]. Interestingly, ECM is not restricted to a structural function and accumulating evidence indicates that a critical balance among the ECM proteins can directly promote or prevent the development of cardiac hypertrophy [62]. CFs also can act upon cardiomyocytes through paracrine interactions by producing a variety of hypertrophic humoral factors (eg, cardiotrophin-1, endothelin-1, and interleukin-6, among others) [63–65]. Endothelial cells, and associated vessel wall components, are additional key elements undergoing important structural and functional changes during cardiac response to stress stimuli in conditions of increased workload. Coronary angiogenesis is very important to preserve myocyte growth and contractile function as neo-vascular could provide more oxygen and energy to hypertrophic myocardium in the remote nonischemic zone. In the early phase of cardiac growth, coronary angiogenesis is promoted by the mTOR-dependent induction of myocardial vascular endothelial growth factor-A (VEGF-A) and Angiopoietin-2 (Ang-2) expression [66]. Failure to maintain the expression of these growth factors contributes to impaired angiogenesis and therefore to the progression from adaptive cardiac hypertrophy to HF [66]. Recently, data from Kazakov and collaborators [67] showed that endothelial nitric oxide synthase (eNOS) of the bone marrow also can contribute to myocardial angiogenesis in pressure-induced cardiac hypertrophy. Thus, the cytoarchitectural pattern of heart remodeling can greatly influence the functional outcome of the heart response to stress and unbalanced contribution of any of the three major cellular components can lead to an inadequate remodeling, leading to HF.

AMPK in the Energy-depleted Failing Heart

There is clear evidence that the failing heart is energy depleted [68–71]. This low energetic potential affects the myocardial contraction/relaxation cycle depending on ATP. In advanced stages of HF, myocardial ATP levels are progressively reduced by 25–35 % [72, 73]. The altered energetic state in HF is complex and likely involves all steps of energy production: substrates utilization, mitochondrial function, and ATP transfer [68, 69]. ATP utilized by the heart results mainly from oxidative phosphorylation in the inner mitochondrial membrane. The catabolism of exogenous substrates provides NADH (nicotinamide adenine dinucleotide, reduced) and FADH2 (flavin adenine dinucleotide, reduced) as donors for electron transport. With regards to substrate utilization, the healthy myocardium has the remarkable ability to switch between glucose and fat as fuel sources [74]. This metabolic flexibility ensures a constant rate of ATP production in diverse physiological and dietary conditions. As already mentioned, long chain fatty acids are preferred substrates under normal aerobic and hemodynamic load conditions. Indeed, their oxidation inhibits glucose uptake and catabolism and vice versa, a reciprocal metabolic control known as the Randle cycle [75, 76]. The Randle cycle is perturbed in HF [77]. Indeed, most experimental and clinical studies show that the failing heart is characterized by a progressive shift in favor of glucose utilization, corresponding to changes in the expression of genes

controlling fatty acid oxidation and mitochondrial biogenesis [69, 70, 77]. However, the decrease in fatty acid oxidation is not compensated by an increase in glucose oxidation, thus leading to metabolic inflexibility and lack of substrate adaptability to the energy needs. Mitochondrial dysfunction underlies this metabolic remodeling. Although the failing heart contains more mitochondria, they are reduced in size and display ultrastructural abnormalities [77]. Defects at specific sites of the electron transport chain impair their oxidative phosphorylation capacity [68, 69]. Fatty acid oxidation is also affected, especially in severe HF, by a decreased content of enzymes that control their mitochondrial transport and oxidation. The expression of genes encoding for these enzymes depends mainly on the PPARγ co-activator (PGC-1α), which is probably the most important transcriptional factor involved in heart mitochondrial biogenesis [78]. The downregulation of PGC-1α expression is decreased in HF and may contribute to energy depletion of the failing heart. However, in two genetic models of PGC1α deficiency, the resulting metabolic disturbances do not lead to HF, except for hearts submitted to chronic pressure overload [79–81]. This indicates that the pathological transition from compensated cardiac hypertrophy to HF implies more than PGC-1α and probably energy depletion. In addition to a deficient oxidative mitochondrial capacity, decreased content and isoform alteration of the phosphotransfer creatine kinase system are also hallmarks of HF [68, 69].

As regards energy depletion, we already mentioned that activation of AMPK protects the heart against cardiac stress such as ischemia by regulating glucose and fatty acid metabolism. Failure to activate AMPK during cardiac stress is associated with decreased cardiac efficiency [13, 15]. However, during transition to HF, physiological AMPK activation seems clearly not sufficient to maintain ATP levels. The failing myocardium is therefore unable to adapt efficiently energy production to utilization.

AMPK in the Transition from Hypertrophy to Failure

AMPK activity is significantly increased during pathological hypertrophy [15, 82]. This phenomenon is considered to be an adaptive response as AMPK activation will antagonize the hypertrophic response. AMPK and its upstream kinase LKB1 not only antagonize the hypertrophic response but also delay the transition to HF by promoting angiogenesis (Fig. 1). Indeed, AMPK activation induces VEGF expression and secretion in cardiomyocytes [45•]. The latter coordinates angiogenesis to hypertrophy in response to pressure overload [45•]. In LKB1-deficient hearts, the lack of AMPK-α2 activation not only decreases energy availability and increases mTOR signalling but also impairs VEGF induction [46, 83, 84]. In this animal model, the disruption of normal paracrine signalling between myocytes and the coronary vasculature favors the transition to HF.

AMPK also directly affects the vascular system. In myocardial vascular endothelial cells, AMPK signaling cascade also regulates VEGF expression and angiogenesis and is reciprocally activated upon VEGF stimulation [85]. This activation loop is critical as dominant-negative AMPK abrogates both endothelial cell migration as well as in vitro differentiation into tubelike structures under hypoxic conditions [86]. The proangiogenic role of the LKB1-AMPK signaling pathway has been demonstrated in vivo, in mice specifically deleted for LKB1 in endothelial cells and submitted to ischemia-induced revascularization [87]. AMPK also controls eNOS activation. eNOS is known to be a direct target of AMPK in cardiomyocytes [88], although the role of this phosphorylation is not known. Recent findings demonstrated that eNOS in circulating bone marrow–derived endothelial progenitor cells (EPC) was identified as a regulator of myocardial angiogenesis and fibrosis in pressure-induced cardiac hypertrophy [67]. In addition to impaired angiogenesis, increased peripheral resistance (myogenic tone) is an additional hallmark of chronic HF [89]. In the acute phase of cardiac remodeling, increased vasoconstriction may serve as a compensatory mechanism for decreased cardiac output to maintain levels of blood pressure required for an optimal circulatory efficiency. However, in the long term, chronic vasoconstriction becomes excessive and may contribute to further progression of HF. AMPK has been shown to participate in the control of vascular smooth muscle contraction by directly phosphorylating and inactivating myosin light chain kinase [90].

Gundewar and collaborators [16••] demonstrated that chronic treatment with the AMPK activator metformin improves left ventricular function and survival in a murine model of HF. The implication of AMPK in this process has been confirmed by using mice lacking functional AMPK. Finally, they showed that two downstream AMPK mediators, eNOS and PGC-1α, participate in the protective action of metformin.

Contribution of the Myocardial Interstitium to the Progression of HF

In addition to myocyte hypertrophy, the hallmark of myocardial structural remodeling is accumulation of a heterogeneous ECM. The highly organized architecture of myocardial interstitium is replaced with a thickened, poorly organized structure that leads to altered myocardial systolic and/or diastolic function [55]. Plasma profiling of ECM proteins may have a role in predicting outcomes of patients in HF. Indeed, higher plasma levels of collagen-derived peptides (procollagen type III amino terminal propeptide [PIPIII]; procollagen type I carboxy terminal propeptide

[PIP]) were associated with increased mortality [91]. Matrix metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMPs) also have shown potential prognostic value with respect to cardiovascular events and mortality. For example, increased plasma levels of MMP-9 remain elevated for 6 months after myocardial infarction and are associated with the degree of left ventricular dilation, which is a predictor of outcomes [92]. Recent findings show that AMPK can suppress MMP-9 expression by inhibiting the nuclear factor kappa beta (NF-κB) pathway in mouse embryo fibroblasts [93]. There are other lines of evidence showing that AMPK could interfere with the production of ECM proteins by preventing transforming growth factor (TGF)–β–induced myodifferentiation of fibroblasts [94]. Finally, AMPK could alter cell–cell or ECM–cell communication in the heart by modulating assembly of cellular junctions, as it does in epithelial kidney cells [95, 96]. Together, these in vitro results suggest that AMPK activators might have therapeutic potential to HF, in terms of cardiac fibrosis.

Conclusions

AMPK possesses numerous substrates involved in various functions including cell metabolism, contraction, architecture, migration, and growth (Fig. 1). By sensing modification of the environment and simultaneously regulating its different targets, AMPK helps the heart to adapt to these changes. These adaptations occur in pathologies like myocardial ischemia, cardiac hypertrophy, and HF. AMPK is naturally activated in such cardiopathies and mainly delays their development and the onset of associated adverse consequences. However, this intrinsic AMPK activation is clearly not sufficient to totally prevent them. For that reason, a potential therapeutic approach would be a pharmacological AMPK overactivation to strengthen and/or to prolong its cardioprotective effects. Numerous animal studies, showing that pharmacological AMPK activation is protective for the ischemic and hypertrophic heart whereas genetic AMPK deletion exacerbates myocardial ischemia/reperfusion and hypertrophic injuries, support this hypothesis. Similarly, pharmacological AMPK activation protects the diabetic heart via its synergistic action on diverse metabolic and nonmetabolic processes.

It has to be noted that the evidence for cardioprotective effects of AMPK in these different pathologies is mainly circumstantial. Indeed, the most frequently used pharmacological agents, including metformin, induce a rather nonspecific AMPK activation by increasing AMP/ATP ratio. The A-769662 compound, a new direct AMPK activator, is also known to have off-target effects. One of the future challenges will be the discovery of new AMPK activators with higher specificity and/or specifically targeting the heart. For example, a study evaluating the effect of a chronic pharmacological and specific AMPK activation during the transition to the failing heart would be worthwhile.

In the same way, animal models used for genetic invalidation of AMPK are whole-body knockout of AMPK catalytic subunits or transgenic mice overexpressing a dominant-negative form of AMPK. These mouse models are not useful to precisely identify the molecular mechanisms involved in the AMPK cardioprotective effects. The generation of tissue-specific knockout animals where AMPK will be selectively invalidated in cardiomyocytes, in endothelial cells, or in fibroblasts will allow to better determine the relative impact of each AMPK action on cardiac pathologies.

Acknowledgments The authors are supported by the Fonds National de la Recherche Scientifique et Médicale (Belgium) and the Actions de Recherche Concertées (Belgium). Dr. Sandrine Horman and Dr. Luc Bertrand are Research Associates of the Fonds National de la Recherche Scientifique, Belgium.

Disclosures No potential conflicts of interest relevant to this article were reported.

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- •• Of major importance

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